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INDIAN DEMOCRACY AT 70

Challenges Ahead

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A matter of Rights amid Wrongs: A case study of Valmikis of Jammu & Kashmir

Pratiba Naitthani

Right to Equality under Article 14 is considered to be the most important Fundamental Right guaranteed to each and every citizen of India, without any discrimination on the basis of caste, color, creed, religion, gender, economic status etc. However, this provision of the constitution is brazenly violated in the state of Jammu & Kashmir. Article 35 A of the Indian constitution allows the state of Jammu & Kashmir to decide the Permanent Residents of the state and those deemed fit by the state are given the Permanent Resident Certificate that is the PRC. It basically extends the benefits of the state services and facilities to those who are PRC holders. It was in 1957 when the SafaiKarmacharisor Sweepers in Jammu and Kashmir went on strike. This strike went on for over one month and hence about 200 scheduled caste persons, Valmikis as they call themselves, were brought to Jammu and Kashmir from Punjab, to work as SafaiKarmacharis/sweepers. Although they were promised PRC, even after living in the state for almost 60 years, these SafaiKarmachris are not given PRC. This has resulted in state invented discrimination against the Scheduled Caste persons from Punjab. They are compelled to live like refugees, without any rights which are enjoyed by the scheduled caste persons elsewhere in India.

This paper attempts to find out the root cause and implications of the blatant discrimination against the Scheduled Caste persons in the state of Jammu &Kashmir. In the largest democracy of the world, such discrimination and exploitation in the name of law are unheard of. Rights can not be selective for one section of the society and not for the other. The soul of Democracy is Equality, Liberty and Justice and it is imperative that the state ensures these for all.

In the absence of any formal references or data available, the researcher made multiple visits to the area and collected most of the information by visiting the field, ie Jammu city, in the Bastis/localities of the Valmikies and by interacting with the community.Interviews both individual and group were conducted to collect information and data. Information was also collected by responses to RTI and referring to the Constitution of India, Constitution of Jammu and Kashmir, books, govt documents andnewspaper reports.

Introduction of the area:

This study was conducted in the state of Jammu & Kashmir. Under the 1st Schedule of Indian Constitution it is the 15th state of India situated in the Northern India. The state currently has three parts namely Laddakh, Jammu & Kashmir. The population comprises of Muslims, Hindus, Buddhists and Sikhs. This study was conducted in Jammu region, where Valmikis,(as they call themselves), the Scheduled Caste personsfrom Punjab, have been living since 1957.

Historical Background:

As India got free from the enslavement of the British, the princely state of Jammu & Kashmir acceded to India on 26th October 1947, with Maharaja Hari Singh, the ruler of this State, signing the Instrument of Accession to join the dominion of India. With the end of hereditary rule in

different princely states in independent India, the democratically elected governments took over the administration, both at the central and at the state levels. The Constituent Assembly formulated the Constitution of India. However,the democratic process of forming a constituent assembly for the state could not be completed in Jammu & Kashmir due to the attack by the Pakistan army on 22nd October 1947, along with the PathanTribals, (Jagmohan, 2014, Rao, 2002) on the state. The situation in Jammu & Kashmir was 'unusual and abnormal', besides, India took the issue of Pakistan aggression to the United Nations on 1st January 1948 and the matter was pending there, hence it was so decided that till the normal life is restored, (N. G. Ayyanger in Constituent Assembly,17th October 1949, Legal Documents, 2016, pp58), a temporary Article be added in the constitution, which originally was Article 306 A, later inserted in the constitution as Article 370. This proposal made by N.G. Ayyanger was accepted by the constituent assembly. Although passed by the constituent assembly, Article 370 was a temporary arrangement, to be in force till situation in the state became normal. It made provisions that the constitution of India will not by default be applicable in the state of Jammu & Kashmir, except for Defense, Foreign Affairs and Communications. Art 370 also allowed modification by the Presidentin the existing laws for the state of Jammu& Kashmir to meet any situation in the absence of a representative body. Thus, for implementation of the Indian constitution in the state a Presidential order with concurrence of the state legislature was required.

Jammu & Kashmir does not have any Special Status:

It is noteworthy that nothing in Article 370 denotes or indicates or mentions that Jammu & Kashmir has been granted any Special Status. In 1950 when the constitution was adopted, Part XXI had the title mentioned in the const as Temporary & Transitional

Provisions. It was in 1962 that the word Special was added in part XXI, for Art 371, (Constitution of India, Bakshi, pp 394). Article 370 is Temporary and not Special, nor does it at any point mention Special Status for Jammu & Kashmir, (Constitution of India). In fact, Article 370 was to be implemented only as long as the Indian Constitution was made applicable in the state, (N. G. Ayyanger in Constituent Assembly, 17th October 1949, Legal Documents, 2016, pp 61),

Article 35 A:

On the pretext to regulate the rights of people in the state, through Permanent Resident Certificate or PRC, a new law was suggested by the then Jammu & Kashmir leadership.Since, Article 370 allowed modifications by the President for the state of Jammu & Kashmir, itpaved the way for Presidential order of 1954. This Presidential orderadded a new provision in the constitution, Article 35 A, which intended to limit the entitlement of rights and privileges of some people within the state.

On 14th May 1954, the President of India issued an order- Constitution (application to Jammu and Kashmir) Order 1954, (Kaul, 2017, pp 07)

After Article 35, the following new article shall be added, namely "35 A. *Saving of laws with respect to permanent residents and their rights: Notwithstanding anything contained in this Constitution, no existing law in force in the State of Jammu & Kashmir, and no law hereinafter enacted by the Legislature of the State –*

- *Determining the classes of persons who are, or shall be, permanent residents of the State of Jammu & Kashmir; or*
- *Conferring on such permanent residents any special rights and privileges or imposing upon other persons any restrictions as respects –*
- *Employment under the State Government;*

- *Acquisition of immovable property in the State;*
- *Settlement in the State; or*
- *Right to scholarships and such other forms of aid as the State government may provide'*
- *Shall be void on the ground that it is inconsistent with or takes away or abridges any rights conferred on the other citizens of Indian by any provision of this Part."*

It is pertinent to note here that under sub section (1) of Article 370, the President of India can issue an order with concurrence of the Govt of Jammu & Kashmir but it neither empowers the President to bring about any amendment to the constitution nor abridge any Fundamental Rights, (Kaul, 2017, pp 09)

Thus, Presidential Order issued for implementing any existing Article cannot be assumed to be the power of President to amend or add a completely new Article in the constitution, without going to the Parliament.The President does not enjoy the power to amend the constitution, under article 368 only the Parliament can amend the constitution, (Bakshi, 2018, pp 392).However,despite clear provisions, Article 35 A was inserted in the constitution through Presidential Order, without referring it to the parliament. This article empowered the state of Jammu & Kashmir to decide whether and individual should be grantedPermanent Residence Certificate.

Section 6 in Constitution of Jammu & Kashmir:

As per the Constitution of Jammu & Kashmir, the definition of Permanent residents in Section 6:

(1) Every person who is, or is deemed to be, a citizen of India under the provisions of the Constitution of India shall be a permanent resident of the State, if on the fourteenth day of May, 1954-

(a) he was a State Subject of Class I or of Class II;

(b) having lawfully acquired immovable property in the State, he has been ordinarily resident in the State for not less than ten years prior to that date.

(2) Any person who, before the fourteenth day of May, 1954, was a State Subject of Class I or of Class II and who having migrated after the first day of March, 1947, to the territory now included in Pakistan, returns to the State under a permit for resettlement in the State or for permanent return issued by or under the authority of any law made by the State Legislature shall on such return be a permanent resident of the State.

(3) In this section, the expression "State Subject of Class I or of Class II" shall have the same meaning as in State Notification No. 1-L/84 dated the twentieth April, 1927, read with State Notification No. 13/L dated the twenty seventh June, 1932. (Constitution of Jammu and Kashmir, pp 3 and 4)

(The term "State subject" means and includes —

Class I.— All persons born and residing within the State before the commencement of the reign of His Highness the late Maharaja Gulab Singh Sahib Bahadur, and also person who settled therein before the commencement of samvat year 1942 and have since been permanently residing therein.

Class II—All persons other than those belonging to Class I who settled within the State before the close of samvat year 1968 and have since permanently resided and acquired immovable property therein.)

Thus, it is absolutely the prerogative of the State legislature to define the Permanent Resident and thus, enable a person to enjoy the rights he is entitled to as a citizen of India. The problem with Article 35 A is also its origin, it has been created under Article 370 which itself is a Temporary provision. Despite all the controversies, Article 35 A thus far has prevailed and has been

instrumental in the formation of laws pertaining to the Permanent Resident Certificate under the constitution of Jammu & Kashmir.

Article 35 A is basically misuse of provisions of Article 370 because it was added in the Indian constitution without the involvement of Indian Parliament. Article 35 A violates the constitution of India as no organ or authority can amend/delete/modify/change/add anything in the constitution except for the Indian Parliament. It is also a violation of the basic principles and rights enshrined in the Preamble of the Constitution. As a result of the implementation of Article 35A, lakhs of Indian citizens have been deprived of "JUSTICE, social, economic and political" and "EQUALITY of status and of opportunity". It has also failed to "promote FRATERNITY assuring the dignity of the individual and the unity and integrity of the Nation", enshrined in the Preamble to the constitution of India, (Bakshi, 2018, pp 1)

The case of Valimikis in Jammuand Kashmir:

It was the dream of Dr. Ambedkar to give equal rights and equal status to the scheduled caste persons, the downtrodden section, to the suppressed and exploited sections of the society. His dream was shared by the leaders of India, who aspired to guarantee Liberty, Equality and Justice to all, without any discrimination on any ground. In order to fulfill this dream, fundamental rights were guaranteed to all, there has been consistent endeavour to uplift the downtrodden sections of our society. Irrespective of the state or region they live in, all the scheduled caste persons are entitled to certain special rights and privileges, to bring them at par with the rest of the society. However, considering the sub human condition of the Valmikis on in Jammu and Kashmir, this dream of Dr. Ambedkar, has no significance. They live in appalling condition with no rights, no human dignity and no hope for a better future.

The researcher made three visits to Jammu in a span

of one year. The first visit was to understand and explore the reality of the problems described, followed by basic interaction with the Valmikis. In the next two visits detailed group discussions were held to discuss various aspects of the issues and problems of the Valmkis. The personal visit to the Valmikis settlement also gave an insight into the subhuman conditions this community lives in. In three visits to Jammu to meet the Valmikis. The participants consisted of Males and Females, though the number of males was larger than the females. The age of participants varied from few above 60, some between the age of 40-60 years and majority between 20- 40 years. In the age group between 40-60 years, few were uneducated, few had studied up to 8th to 10th Std, whereas in the age group between 20-40 years all were educated and some had degrees like, M. A., M. Com., M. Sc., C. S., B. A., B. Sc. etc.

About 15,000 people, who call themselves Valmikies, live in Jammu, they belong to the Scheduled Caste. Their forefathers were brought to Jammu from the state of Punjab by the govt of Jammu and Kashmir. The Valmikis of Jammu are a glaring example of modern-day slavery. They live in abject poverty and deprivation, inflicted by the laws of the state. They are compelled to live in sub human conditions, like refugees, stripped of all Fundamental Rights, in their own country because they do not have the PRC. Since they are not PRC holders, the state literally does not even acknowledge their existence. It is shocking that the state rules prevent them from taking up any job other than that of a sweeper in the Jammu Municipal Corporation. They are not even entitled to promotion despite 25-30 years of serving as a sweeper. Professional education and govt jobs are far fetched dreams for the Valmikis. Owning a house and property, voting in the elections, enjoying the benefits of govt schemes is beyond their imagination. It is disturbing that in 21st Century, in the largest Democracy in the world, there is a section of citizens, which is not only denied human rights, but denied the very right to existence.

Following is the study of the Valmikis, their past, their struggle for survival and the current condition.

The Strike of SafaiKarmacharies:

It was in 1957 the SafaiKarmacharis or sweepers of the state of Jammu & Kashmir went on a month-long strike. This resulted in piles of garbage and filth accumulating in Jammu, creating a danger of breakout of an epidemic. The then Prime Minister BakshiGhulam Mohammadin the cabinet meeting decided to bring the scheduled caste persons as SafaiKarmacharis or sweepers to Jammu from the neighbouring state of Punjab. They were brought from Amritsar and Gurudaspur. The government of Jammu & Kashmir promised them that the PRC rules will be relaxed to accommodate them and thus the Valmikis settled in Jammu. The bastis/ settlements of Valmikies were mainly in three areas, Valmiki Colony in Gandhi Nagar, Christian Colony in Bakshi Nagar and Dogra Hall in Reshamgarh. In those days these areas were far from the city and were more or less deserted. In these bastis they were provided with free water and electricity connections along with houses to live in. The Valmikis started work without any further delay and cleared the city of Jammu of the garbage and filth piled up for over a month.

The denial of rights and legal glitches:

According to Article 35 A the power to grant PRC is with the Jammu & Kashmir legislature and since the Valmikis were brought to the state after 1944 as per the rules of PRC they are not entitled to be state subjects/ permanent residents and hence the PRC is not issued to the Valmikis. Although the Valmikis from Punjab came and settled permanently in Jammu & Kashmir, for two generations they did not realisethat the PRC was not given to them. Nor did they understand the implications of not having the PRC. According to the respondents the first two generations carried forward the legacy of being

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just a sweeper. However, the third generation started getting educated and since now they were educated, they planned to take up jobs other than being a sweeper in the municipality of Jammu. The Valmikis got a nasty shock when they were told that despite being educated, they cannot take up any jobs other than as a sweeper as they do not have the PRC. Things got worst when they were told that not only, they are ineligible for any government jobs being Non-PRC holders, but they can take up a job only as a sweeper, that too only in the Municipality of Jammu, because this is the legal provision. In the absence of PRC, they are living a life without any rights, privileges and dignity. It is a life of misery and exploitation.

Discussion and Analysis:

The sufferings and challenges of Valmikis:

While discussing their sufferings, issues, problems and challenges the members of the Valmiki community expressed their plight and helplessness and raised many thought-provoking questions. They described their problems and discussed the struggle of survival so far.

The general views expressed by the respondents were that 'India is a democracy, all have equal rights, then how can one state of the country make such discriminatory laws and deprive a particular, vulnerable section of the society of its basic human rights? How can a law be created to ensure that the depressed class remains depressed and is consistently exploited? How can the law create compulsions of deprivation and suppression of a community? Why are we denied any growth, progress, education and human dignity? Today everyone is fighting for the rights of the Rohingyas, they are foreigners, they are refugees, but since last 60 years we are deprived of our fundamental rights in our own country, we are denied human dignity, we have been running from pillar to post but no one is listening to us,

no one is even considering our plea, what kind of activism is this?'

Caste based discrimination, exploitation and deprivation:

The male members were more articulate while expressing themselves. The leader of the Valmikis Gharu Bhatti said that 'nowhere, in the country the Scheduled Castes face such discrimination and ill-treatment like Jammu & Kashmir. This is the only state where the law discriminates against the Scheduled Caste persons. We did not come here forcefully, nor did we come here as refugees, we are requested by the Jammu & Kashmir govt to come here and clean the month-old filth. We were promised PRC but 60 years have gone by, we did not get anything. We are living here since 1957, but we cannot buy property, we cannot start business, nor can we get good education and good jobs. Since we do not have PRC, we are not given the Scheduled Caste certificate. Due to which we do not get any reservation in education or employment, nor do we get any benefits of state or center schemes, which are available to other Scheduled Caste persons in the entire country. Many of us can't even get the BPL (Below Poverty line) cards, meant for the poor section of the society. This is the only state where the law ensures that the exploited remains the same, he must get more exploited, he should not grow and flourish. He must remain deprived.'It was indeed shocking to hear these revelations by the community. In the absence of a Caste Certificate, not only in Jammu and Kashmir, but anywhere in India, they cannot avail of any benefits extended to the Scheduled Caste persons in India. It was ironical to see that some of those, who had relatives on Punjab, compared their socio-economic conditions with their relatives, who had access to reservations in education and employment and were well to do compared to those living in Jammu and Kashmir.

but we cannot get a bigger house. Four generations are compelled to live in single room.' This was evident from the condition of their houses and the extremely narrow lanes of their settlement. Since they are not allowed to buy property, reconstruct or even renovate the houses given by the state, they cannot grow horizontally. Hence, they are growing vertically, by building more floors above the existing house. The condition here is dangerous, as these added floors are not cemented, hence are unstable, besides, the ground floor walls are developing huge cracks because of the weight of the added floors. The unreasonable restrictions are compelling the Valmikis to live in dangerous conditions.

Poor living conditions:

It is indeed true that there are no proper roads in Valmikibastis/settlements. They clean the drainage of the entire city but there are no proper drainages and hence during the rains the dirty water of the drains enters their houses. The high voltage electric wires are hanging so low that it can touch people while walking on the streets. They have filed complaints many times but it falls on deaf ears. No one comes even to check the poor and dangerous conditions they are living in.

Denial of voting rights:

One of the respondents raised the issue of denial of voting rights to the Valmikis, he said that 'We are bound to work as sweepers only in the municipality, but see the irony, we cannot contest municipality elections, in fact we are debarred from even voting in the municipal elections. Since we have no voting rights, we have no voice in the local management of the basti and hence, no one pays any heed to out problems. Similarly, we cannot vote in the state legislature/ state assembly elections, hence no MLA or politician is bothered about us. We do not exist for them, because we cannot vote for them.'

Denial to join Central Services:

A young respondent, now a petitioner in the Public Interest Litigation filed in the Supreme Court, challenging 35 A, shared her experience. She said that 'We cannot join any central govt services, like the armed forces, BSF etc because we do not have PRC.' She wanted to join the Border Security Forces, BSF, a security service under the central govt. But being a non-PRC person, she was denied the job. She added that the govt has various schemes for the girl child, but they cannot avail of any of the central or state schemes for the girls. Even the benefits under the National SafaiKarmachariare denied to them.

'The political parties which thrive on Dalit Politics, are not bothered about us because we are very small in numbers. We are citizens of India, then why are we denied our fundamental rights? The laws of this state ensure that we remain backward, clean their filth and remain deprived of basic rights.' Said one of the respondents. 'A scheme in collaboration with the National SafaiKaramcharis Finance andDevelopment Corporation and the Ministry of Social Justice andEmpowerment was launched in J&K for the socio-economic growth of safaikaramcharis, but Valmikis cannot take its benefit because they are not thepermanent residents of J&K.' (Manhotra, 2015)

The Struggle of the Valmikisso far:

With passing years, the Valmikis realized that just crying foul is not the solution. If they want their rights and dignity back then they must organize themselves and take concrete measures. Thus, came the idea of forming area wise organizations. The Valmikis Valmiki Mohalla Trust was formed in Gandhi Nagar in 1996 and now all the activities through this organization. They elect their president. The organization deals with local issues like water and electricity supply, ration cards, Adhar cards, other amenities etc. Similarly,

theValmikis in DograMohalla have formed the Valmiki Sadar Sabha.

In the year 2006 the Valmikis submitted a Memorandum to the Law Minister Jammu & Kashmir, highlighting their plight and drawing the attention of the govt towards the injustice done to the community. Following are the excerpts from the Memorandum-

'That apart from the restriction in govt employment for the SafaiKarmacharis, the colony of the safaikarmacharis, ie Christian Colony, bakshi Nagar, Dogra Hall, Reshamgarh, Valmiki colony Gandhi Nagar, has not been regularized till date, it is pertinent to mention here that as per the communication number JDA/VC/331/34/PS dated 20-08-2004, 30 colonies were recommended by the Vice Chairman, Jammu Development Authority for regularization, but surprisingly this issue of colonies of safaikarmacharis has been ignored by the Housing and Urban development department.

Pension benefits were extended to the SafaiKarmacharis by the govt vide order no 285.HUD/LSG of 1995 dated 29-09-1995, should be extended to the safaikarmacharis.

Govt order no 205 of 1962 dated 02-06-1962 grant of lease of plots of land measuring 3 Marlas in favour of Gorkhas and Bazigars on payment of ground rent, without charging any premium and relaxing the rule to produce PRC for the same has not been extended to the SafaiKarmacharis. Neither their colonies are regularized nor are they given any land. It is humbly submitted that state subject to be issued or state subject conditions may be relaxed in favour of the safaikarmacharis.'

GharuBhatti, the leader of the Valmikis in Gandhi Nagar has been tirelessly working to get justice for his community. On 16th December 2017 he wrote an open letter to the govt of Jammu & Kashmir. Some of the points raised in his open letter express the desperation of the community:

"Our Plight is presently so grievous that:

- *We don't have security of ownership of the houses that we have occupied for approximately 6 decades,*
- *We can't avail our fundamental rights which should be guaranteed to us as citizens of India,*
- *Our children have no right to obtain higher (professional and technical) education in the State where we have lived in for three generations,*
- *We are discriminated against in the matter of securing government jobs even though we have the requisite qualification,*
- *We have become bonded laborers in the State confined to garbage collection and sweeper work, which amounts to slavery of a sort.*
- *To crown it all, our greatest peril lies in the fact that the State has (contrary to national and international human rights law) thwarted out any mechanism or procedure for us to achieve our fundamental rights, by implementing a farce called "Permanent Resident Certificate".*

In the year 2015 a Public Interest Litigation was filed in the Supreme Court, challenging the constitutional validity of Article 35 A, which makes provision for the PRC. The community is very optimistic about the outcome of the P I L.

Besides this, they have now started talking to the media, they go to attend different conferences and seminars, so that the people at large get to know about their sufferings.

What do the Valmikis lose?

It is a known fact that due to Article 370, which despite being temporary, is still in effect, all the provisions of the

Indian Constitution are not implemented in the state of Jammu & Kashmir and hence the people of this state do not enjoy the fruits of all the provisions of Indian Constitution, unless accepted by the Assembly of Jammu & Kashmir. However, considering the fact that the Valmikis were brought to Jammu & Kashmir from Punjab, it is pertinent to list out the benefits and privileges which they would have enjoyed had they remained in Punjab.

The blatant violation of Fundamental Rights:

In the absence of the PRC the Valmikis are denied the Fundamental Rights, guaranteed to all the citizens of India, without any discrimination on any ground. Listed below are the rights violated/ denied to the Valmikis in Jammu & Kashmir-

Sl.No	Article No.	Provisions
1	Article 14-	Equality before the Law and equal protection of the law.
2	Article 15-	Equality of Status
3	Article 16-	Equality of Opportunity. Special provisions for the reservation in employment.
4	Article 17-	Prohibits Untouchability
5	Article 19-1 (g)-	Right to choose profession, trade, business
6	Article 20-	Right to Life (Livelihood)
8	Article 23-	Right Against Exploitation
9	Article 29-	Cultural and Educational Rights

The Constitution of India makes the following provisions for the persons belonging to Scheduled Castes:

Sl.No	Article No.	Provisions
1	Article 15 (4)	Reservation in Educational Institutions
2	Article 15 (5)	Reservation in Pvt. Educational

		Institutions
3	Article 16 (4)	Rreservation in Govt Employments
4	Article 16 (4A)	Reservation in Promotions
5	Under Article 38	State should secure social order for the promotion of welfare of people
6	Article 46	The educational and economic interest of the Scheduled Casts and Scheduled Tribes be protected and promoted
7	Article 243 D	Reservation of seats for Scheduled Castes in Panchayats
8	Article 243 T	Reservation of seats in Municipalities
9	Article 325	Prohibition of Disenfranchisement in election, based on caste, religion,sex etc
10	Article 330	Reservation of seats in the Lok Sabha
11	Article 332	Reservation of State Legislative Assemblies
12	Article 335	Requirement of state to acknowledge the claims of Scheduled Castes/Scheduled Tribes while making appointments to posts and services

Some of the Missed Opportunities:

Education Related Provisions-

Pre-Matric Scholarship to SC Student

Pre-Matric Scholarship to the Children of those engaged in occupations involving Scavenging, Tanning and Flaying cleaning and prone to health hazards

Post Matric Scholarship for Scheduled Caste Students (PMS-SC)

Scholarships for obtaining Higher Education and Coaching Scheme- full financial support for –

1- IITs, NITs, IIMs, reputed Medical/Law and other institutions

2- National Fellowship for M. Phil, Ph. D and equivalent research degrees

3- National Overseas Scholarship- for Master's degree and Ph. D.

4- Free Coaching for SC and OBC Students

Schemes for Economic Empowerment of Scheduled Caste Persons-

- Punjab Scheduled Castes Land Development and Finance Corporation-
- Punjab Scheduled Castes Land Development and Finance Corporation (PSCFC) works towards improving economic conditions of the members of the Scheduled Castes (SC) in the state.
- National Scheduled Castes Finance and Development Corporation (NSFDC) especially for B P L category
- National SafaiKaramcharis Finance and Development Corporation (NSKFDC) for the SafaiKarmacharis and their dependents
- Special Central Assistance (SCA) to Scheduled Castes Sub-Plan (SCSP)
- Scheme of Assistance to Scheduled Castes Development Corporations (SCDCs)
- Venture Capital Fund for Scheduled Castes
- Credit Enhancement Guarantee Scheme for Scheduled Castes.

Despite repeated petitions by the Valmikis to the state and central govt regarding the violation and denial of rights, no action has been taken so far.

Conclusion:

Preamble to Indian constitution is based on the principles of Equality, Liberty and Justice. The rights are guaranteed to all without any discrimination. But the Valmikis in Jammu & Kashmir are denied the rights andthe ideals of Equality, Liberty and Justice mean nothing to them. Because, they are marginalized, they do not exist for anybody. The politicians pay no heed to their demands as their number is very small. Those swearing by the teachings of Dr. Ambedkar, are not even aware of the subhuman conditions of the Valmikis. The human right activists, running from one court to another, from one media house to another, crying foul when the army takes action against the terrorists; have nothing to say about the systematic exploitation and denial of rights to the Valmikis, created by law and implemented by the govt. NoSuo-moto actions are taken by judiciary. The Dalit rights activists are busy shaping up their political career, but they have no time or inclination to stand by the Valmikis in Jammu &Kashmir, even when the Valmikis have come out in the open and have gone to the court challenging this discriminatory law, not even a single statement has been made to support this extremely marginalized, suppressed and exploited community.

Four generations have suffered at the hand of the center and state laws, they have been deprived of fundamental rights, overall growth, development and prosperityand above all they lost human dignity. How will the loss of four generations be compensated?It is important to note the fact that the Valmikis were brought to help the state and the people of Jammu and Kashmir. Instead of being rewarded the community is punished, not one but four generations have led a life of misery, denial and dignity in their own country. The valmikis

are victims of state managed, systematic discrimination and abuse. It is the legislature that has deprived the Valmikis of their rights, it is ironical that the corrections to be made by the legislature are reaching the Judiciary. The onus is on the center to get their dignity back and on the state of Jammu and Kashmir to make necessary changes in the state laws to give them their rights.

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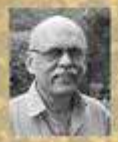

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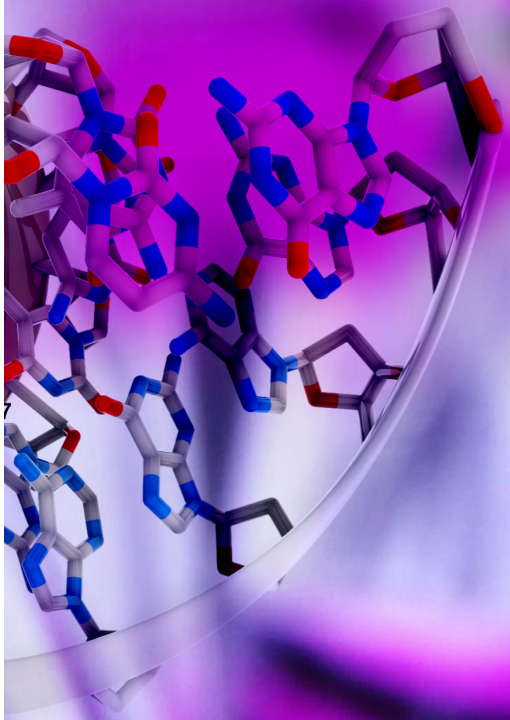

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CHAPTER 2

Taxol To Nanotaxol: A Journey Towards Enhanced Drug Delivery

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Abstract: Drug delivery in the field of cancer has undergone a continuous revolution over the past few decades. Development of novel chemotherapeutic agents without the method of delivering them to the tumor site would find no practical application in uprooting the fatal disease of uncontrolled cell proliferation, cancer. This makes the development of drug carriers exceedingly essential for diagnostics and therapy alike. Nanotechnological science has gained impetus in the recent past and has found applications in a plethora of fields. It has managed to create an impact in the field of diagnostics, drug delivery and therapy, equally. Taxol®, a chemotherapeutic agent that was initially obtained from the bark of *Taxus brevifolia*, moved on to the semi-synthetic approach for its synthesis to address the shortage of its natural source. This drug is partially soluble in water and its initial formulation with Cremophor EL manifested as anaphylactic reactions. To do away with these problems and others such as lower circulation time in blood and non-specificity, nanotechnology is now being looked at as a promising solution. Nanotechnological carriers aim at enhancing target-specificity by functionalization, drug stabilization and preventing its degradation due to physiological conditions, pH, enzymes, etc., demonstrating an Enhanced Permeability and Retention (EPR) effect, prolonged blood circulation and thus better anti-tumor activity, while the side effects being almost negligible. The patents in this chapter aim to highlight how nanotechnology can find practical applications and how one or more than one drugs could be administered *in vivo* in a sustained fashion. The step-wise development in using this potent anticancer drug (Taxol) involved the use of human serum albumin associated compositions (Abraxane®), cremophor-free formulations (Capxol™, Genexol-PM™), numerous oil-in-water emulsions, liposomes and micelles, use of graphene quantum dots (GQDs) for bioimaging and drug delivery and the use of single-walled and multi-walled carbon nanotubes. It also allows the readers to explore nanodevices that can be turned on and off as and when the need be for localized drug delivery. Enabling the nanocarriers to modulate the pharmacokinetic and pharmacodynamic properties of the drug is another notable feature that some of these nanocarriers possess.

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Atta-ur-Rahman and Khurshid Zaman (Eds.)

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1. INTRODUCTION

A normal cell, when developing a neoplastic behaviour, adopts the 6 hallmarks of cancer, turns tumorigenic and may exhibit malignancy. Withstanding cell death signals while sustaining the proliferative ones, eluding growth suppressors, induction of the process of angiogenesis, actuating invasion and promoting metastasis and thus enabling the cells to attain immortal replication ability are the six prominent hallmarks of cancer that the cells adopt [1]. In the developed and the developing countries, cancer is the first and the second leading cause of death, respectively [2]. According to the GLOBOCAN project which is an initiative by The International Agency for Research on Cancer (IARC), the world witnessed 12.7 million cancer cases in the year 2008 [2], while the numbers increased to 14.1 million in the year 2012 [3]. The number of deaths resulting from succumbing to cancer also saw a rise from 7.6 million in the year 2008 [2] to 8.2 million in 2012 [3]. This alarming rate of falling prey to the disease crops up from the present-day sedentary lifestyle, imitation of food and diet fads from the western world and increased tendencies of smoking and alcoholism [2, 4 - 6]. The current modes of treatment available to combat cancer include surgery, employing chemotherapy and radiation therapy in combination or individually, depending on the severity, the type and the stage of cancer [7]. The 1960's witnessed the approval of chemotherapeutic agents like vincristine and vinblastine that were derived from natural sources [8]. The forage for more natural alternatives heightened between the period from 1960-1981, when a collaborative plant screening program was initiated by the National Cancer Institute (NCI) and the U.S. Department of Agriculture (USDA). This program was successful in the collection of about 1,15,000 extracts from 15,000 plant species and their testing which resulted in the identification of a few natural sources for the isolation of molecules that possess potent anticancer activities [9].

Samples from *Taxus brevifolia*, the Pacific yew tree were analyzed by Arthur Barclay, a botanist as USDA. The fruit, needle, twig and bark extracts were tested for their anticancer activity and only the bark extract showed significant cytotoxicity [9, 10]. The bark samples of *Taxus brevifolia* were received in 1964 by two scientists, Mansukh Wani and Monroe Wall, working at the Research Triangle Institute [9, 10]. The bark extract showed potent cytotoxicity against human nasopharynx cancer cell line, 9KB and mouse leukemia cells (*in vitro* cytotoxicity assessment models), while it did not show promising results *in vivo*

[11 - 13]. Following this, attempts to obtain Taxol in its pure crystalline form, begun. In 1966, the active ingredient, that was responsible for the cytotoxic activity, was isolated in its crystalline form. It was named as Taxol in the year 1967 [9, 10], after its source of origin and the presence of hydroxyl groups [9]. Determination of the structure of Taxol required its purified form to be available in large quantities. This was, however, not the case. Twelve kg of stem bark that was air dried could produce only 0.5g of Taxol, the yield being as low as 0.004% [12]. It was also estimated that around 1g of active Taxol could be obtained from three 100-year-old, mature *Taxus brevifolia* trees [11]. With the betterment of the procedures for isolation and purification, the structure of Taxol was elucidated in the year 1971 and reported to be the first compound with a taxane ring possessing antileukemic properties and those capable of tumor inhibition [12, 14]. Although a potential candidate for a chemotherapeutic drug, certain drawbacks of Taxol caused researchers to lose interest in the molecule. Water insolubility of the molecule meant elimination at the formulation stage due to the difficulty in drug delivery [10, 11]. Polyethoxylated castor oil was thus employed for its formulation which leads to various anaphylactic reactions. This was another major cause why the development of Taxol as a chemotherapeutic was looked down at [9]. The inability of total chemical synthesis owing to its complicated structure, complex multistep synthesis procedure, as well as low yields and scarce availability of natural resources for its extraction, further discouraged the drug from reaching advanced development stages [9 - 13, 15]. Also, a low degree of cytotoxicity was identified in P-388 and L-1210 cells and this further dampened the interests [12, 13]. For about a decade, the investigations in this field were at a standstill.

The excellent cytotoxic activity of Taxol against murine B16 melanoma (relatively resistant) and xenografts of human tumors introduced into nude mice when brought to light, furthered its development and it advanced from the preclinical stage to the animal toxicology study stage [10, 12, 13]. Its unique mode of action enthralled the researchers and they were motivated to work towards developing this molecule into a promising chemotherapeutic drug. Taxol promotes the process of microtubule assembly by stabilizing tubulin, thus inhibiting cell division, by preventing the disassembly of the microtubules [9 - 11, 15 - 17]. It does so by causing a shift in the equilibrium towards microtubule assembly by the elimination of the lag period that precedes the process [15, 18]. Taxol interacts with β-tubulin at a specific site (a binding pocket) constituting of β-strands and α-helices [11, 19, 20]. The cells are seen to be arrested in the G2/M phase of the cell cycle, post binding of Taxol to the binding site, not enabling the mitotic spindle to de-construct [11, 15, 18, 20]. Reports on activities of Taxol other than that on microtubules highlight its ability to alter cellular signalling cascades by activation of molecules like Raf-1, nitric oxide synthase and kinases

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भूमिका

'एक और द्रोणाचार्य' वर्तमान शिक्षा जगत का आईना है। नाटक में आदर्शवादी शिक्षकों की लाचारी, अकर्मण्य छात्रों की उच्छृंखलता, छात्राओं की विवशता तथा खरपतवार की तरह उग आई शिक्षण संस्थाओं की मनमानी और शिक्षकों के परिवारों की बेबसी को भी बड़ी शिद्दत से रेखांकित किया गया है। शिक्षकों की लाचारी के लिए उनकी मध्यमवर्गीय मानसिकता को, छात्रों की उच्छृंखलता के लिए उचित मार्गदर्शन एवं 'मोटिवेशन' की कमी तथा शिक्षण संस्थाओं की मनमानी के लिए उनके संचालकों की अत्यधिक महत्वाकांक्षा को जिम्मेदार माना गया है। छात्राओं की विवशता के लिए उचित प्रोत्साहन की कमी तथा शिक्षकों की पत्नियों/गृहिणियों की बेबसी के लिए उनके द्वारा घर चलाने के दबाव को जिम्मेदार माना गया है।

शिक्षकों की लाचारी को दूर करने के लिए उन्हें मध्यमवर्गीय मानसिकता से उबरना होगा। छात्रों की उच्छृंखलता को दूर करने के लिए उनके समक्ष आदर्श व्यक्तित्व की स्थापना करनी होगी। शिक्षण संस्थाओं की मनमानी रोकने के लिए सरकार को जी.डी.पी. का कुछ और अधिक प्रतिशत धन, शिक्षा पर खर्च करना होगा। साथ ही शिक्षा को राजनीतिकरण से बचाना होगा। छात्राओं को और अधिक कानूनी जागरूकता तथा प्रेरणा प्रदान करनी होगी। शिक्षकों की गृहिणियों को आर्थिक आत्मनिर्भरता प्रदान करनी होगी। तभी एकलव्यों के अंगूठे कटने से बचाए जा सकते हैं। आज एक ऐसे द्रोणाचार्य की आवश्यकता है, जो प्रतिभाओं के विकास के लिए दुर्व्यवस्था के विरोध में खड़ा हो।

■ भगवती प्रसाद उपाध्याय

कथानक

कथानक नाटक का एक महत्वपूर्ण तत्व होता है। यह नाटक के कथासूत्र को आगे बढ़ाता है। 'एक और द्रोणाचार्य' नाटक की कथावस्तु वर्तमान शिक्षा जगत एवं महाभारतकालीन गुरुकुल परंपरा से संबंधित है। नाटक की शुरुआत प्राइवेट कॉलेज के प्रोफ़ेसर अरविंद तथा उसकी पत्नी लीला की घरेलू बातचीत से होती है। लीला की बातों में पति को सिगरेट के टुकड़े ऐश-ट्रे में डालने की नसीहत दी जाती है। शक्कर के भाव, राशन-कार्ड बनाने की बातें, माँ के ऑपरेशन की चिंता आदि का जिक्र लीला पति अरविंद से करती है। बातों-ही-बातों में लीला प्रोफ़ेसर अरविंद से प्रश्न पूछती है कि आपने सिन्हा के अफसर के बेटे के अंक बढ़ाए या नहीं? इस पर प्रोफ़ेसर अरविंद कहता है कि लड़का पास होने लायक नहीं था, ''मैं जबरन छात्र को पास नहीं कर सकता।'' ऐसा सुनकर पत्नी लीला अपने पति अरविंद को ताने मारती है। यदि तुम किसी छात्र के अंक बढ़ा नहीं सकते, तो दूसरों का अहसान क्यों लेते हो? दरअसल, सिन्हा के अफसर ने ही अरविंद को नौकरी पर रखवाया था। इसीलिए लीला अपने पति अरविंद से कहती है, ''यदि दो अंक बढ़ा देते, तो कौन-सा आसमान फट जाता!''

उधर प्रोफ़ेसर अरविंद का दोस्त 'यदु' लीला से कहता है कि जानती हो, इसने आज कॉलेज प्रेसिडेंट के लड़के राजकुमार को ही नकल करते हुए धर दबोचा। लीला को 'यदु' बताता है कि वह शहर का सबसे बड़ा गुंडा है। इस पर लीला अरविंद से पूछती है - ''तुम्हें क्या गरज पड़ी थी, नकल करने देते। क्या बिगड़ जाता?'' प्रोफ़ेसर अरविंद सफाई देता है कि वह देखकर मक्खी नहीं निगल सकता। दरअसल, वह एक ईमानदार आदमी हे। सिद्धांतवादी आदमी है। 'यदु' भी अरविंद की

भगवती प्रसाद उपाध्याय

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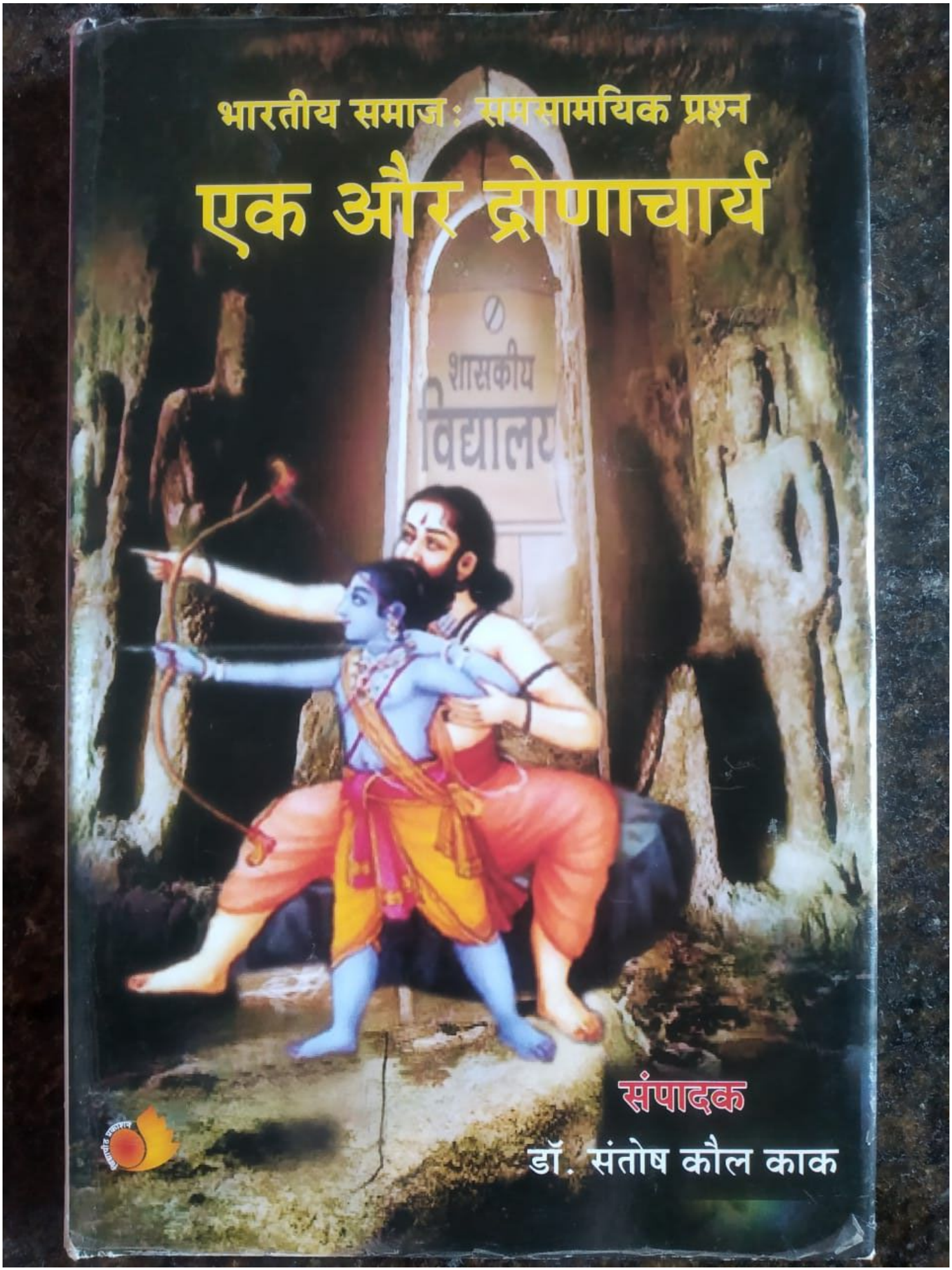

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डॉ भगवती प्रसाद उपाध्याय

'एक और द्रोणाचार्य' नाटक शंकर शेष ने लिखा है। यह एक लघु नाटक है। इसे पूर्वार्ध तथा उत्तरार्ध दो अंको में लिखा गया है। रचना में पौराणिक पात्र द्रोणाचार्य के चरित्र को नवीन संदर्भों में प्रस्तुत किया गया है। साथ ही द्रोणाचार्य के पारिवारिक पात्रों और व्यवस्था से संबंधित अन्य पात्रों का भी नवीन दृष्टिकोण से चित्रांकन किया गया है। अरविंद इस नाटक का प्रमुख पात्र है।

महाभारत में जो स्थान और जो स्थिति द्रोणाचार्य की थी,लगभग ठीक वही स्थान और वही स्थिति इस नाटक के पात्र अरविंद की भी है। अरविंद की मानसिक और पारिवारिक स्थिति द्रोणाचार्य की उन्हीं स्थितियों से मेल खाती है। अरविंद द्रोण से, लीला कृपी से और अनुराधा द्रौपदी से मेल खाती है।

अरविंद एक प्राइवेट कॉलेज में प्रोफेसर है। वह मूल रूप से एक सिद्धांतवादी व्यक्ति है। प्रोफेसर अरविंद सत्य और न्याय का पक्षधर है। परीक्षा के दौरान संस्था के प्रेसिडेंट के पुत्र राजकुमार को नकल करते हुए प्रोफ़ेसर मिश्रा रंगे हाथों पकड़ लेते हैं। प्रेसिडेंट का पुत्र छुरा सामने रखकर नकल कर रहा था। चंदू की रिपोर्ट यूनिवर्सिटी को भेज दी गई क्योंकि उसके पिता प्रेसिडेंट के राजनीतिक प्रतिद्वंदी हैं। चंदू चाहता है कि राजकुमार की रिपोर्ट यूनिवर्सिटी को भेजी जाए। चंदू प्रोफेसर अरविंद के घर जाकर प्रार्थना करता है कि राजकुमार की रिपोर्ट यूनिवर्सिटी भिजवाई जाए। ऐसा न करने पर वह सभी छात्रों के साथ मिलकर धरना प्रदर्शन, आंदोलन, हड़ताल तथा परीक्षा के बहिष्कार की बात करता है। प्रोफेसर अरविंद उसकी बातों से सहमत होकर राजकुमार की रिपोर्ट विश्वविद्यालय भिजवाने की तैयारी करते हैं। अरविंद की पत्नी लीला प्रोफेसर

साहब को ऐसा न करने की सलाह देती है। दरअसल उन्हें अपना परिवार चलाना है।

प्रोफेसर अरविंद का दोस्त 'यदू' भी उनको सलाह देता है कि वह स्वयं अपने प्रिंसिपल बनने का रास्ता साफ करें। कुछ समय बाद प्रेसिडेंट प्रो. अरविंद के घर जाकर उनसे राजकुमार की रिपोर्ट विश्वविद्यालय न भेजने का दबाव डालता है। उधर प्रोफेसर अरविंद अपने फैसले पर अडिग है। प्रेसिडेंट साहब कहते हैं, ''जरा सोचिए तो इस घटना से मेरी पब्लिक इमेज को कितना धक्का पहुँचेगा।

चुनाव का टिकट हाथ से जाता रहेगा।''[१] ऐसा कहकर प्रेसिडेंट साहब प्रोफेसर अरविंद को प्रिंसिपल के पद का लालच देने लगते हैं, ''यू आर ओनली प्रोफेसर टु हूम आई रेस्पेक्ट सो मच।कुछ मामलों में आपसे विरोध हो सकता है परंतु इसका मतलब यह नहीं कि आपकी योग्यता के बारे में मैंने कभी शक किया है।''[२]

उधर प्रोफेसर अरविंद की पत्नी लीला भी उन्हें बहुत समझाती है कि, ''इस बदतमीज लड़के का साथ देकर क्या मिलेगा? प्रेसिडेंट से दुश्मनी ठन जाएगी। किस के भरोसे लड़ोगे? तुम्हारे सहयोगी भी तुम्हारा कहाँ साथ दे रहे हैं।''[३] प्रोफेसर अरविंद कहता है,''लेकिन चंदू को दगा देने का मतलब समझती हो? नकल का विरोध करने वाले सैकड़ों विद्यार्थी मेरे खून के प्यासे हो जाएंगे, मुझ पर थूकेंगे।''[४] प्रो. अरविंद की पत्नी लीला का चरित्र यहाँ महाभारत के द्रोणाचार्य की पत्नी कृपी की याद दिलाता है। वह कहती है, ''प्रेसिडेंट उनसे निपट लेगा। तुम्हें सुरक्षा देगा। प्रिंसिपल बना देगा और यह लड़के तुम्हें सड़कों पर खड़ा कर तमाशा देखेंगे। उनका साथ देने से क्या फायदा।''[५] अर्थात उसे अपना परिवार चलाना है, आदर्श को त्यागकर वह यथार्थ के धरातल पर खड़ी रहकर सोचती है।

प्रो. अरविंद का दोस्त यदू भी उसे समझाते हुए कहता है,''समझने की कोशिश क्यों नहीं करते? पूरे शहर में अफवाह है कि तुमने लड़कों को भड़काया है। पूरा स्टाफ हैरान है तुम्हारी हरकत पर। उधर राजकुमार और उसके साथी भी तुमसे बेहद नाराज हैं। एक तो राजकुमार को पकड़कर तुमने उन्हें चुनौती दी है दूसरे चंदू का साथ देकर तुम उनकी सत्ता ही खत्म कर देना चाहते हो। अगर ये लोग विमलेंदु की हत्या कर सकते हैं तो तुम्हारी क्यों नहीं। हर बात तुम्हारे खिलाफ पड़ रही है। जाओ रिपोर्ट वापस ले लो।''[६]

इस पर पत्नी लीला को लगता है कि प्रोफेसर अरविंद के प्रिंसिपल बनने में ही भलाई है। इस तरह वह व्यावहारिक दृष्टि से सोचती है। साथ ही यदू का दृष्टिकोण भी

बिल्कुल व्यवहारिक है। वह पुन: कहता है कि, ''प्रिंसिपल बन जाओ और वाइस प्रिंसिपल के लिए मेरा रास्ता बनाओ। तुम प्रेसिडेंट का साथ दोगे तो वह भी तुम्हारा साथ देगा। चंदू और उसके साथियों से वह खुद निपट लेगा। लेकिन राजकुमार तुम्हें जिंदा नहीं छोड़ेगा।''[७] इससे पता चलता है कि ईमानदार व्यक्ति को किस प्रकार फँसाया जाता है। इतना ही नहीं प्रोफेसर अरविंद जैसे व्यक्ति को सेंडविच बनाकर दोनों ओर से दबाया जाता है। यदु कहता है,''रिपोर्ट बदलने के अलावा तुम्हारे पास कोई चारा नहीं है। राजकुमार का विरोध करोगे तो हत्या, चंदू का विरोध करोगे तो सामाजिक हत्या। हत्या से तुम बच नहीं सकते।''[८] इस तरह नकलची और प्रभावशाली विद्यार्थियों के बीच एक सिद्धांतवादी ईमानदार प्रोफेसर सैंडविच बन कर रह जाता है।

अंतत: प्रेसिडेंट द्वारा प्रोफेसर अरविंद को प्रिंसिपल बना दिया जाता है। प्रोफेसर अरविंद न चाहते हुए भी प्रलोभन का शिकार हो जाता है। प्रिंसिपल बनने के बाद उसे बंगला तथा अनेक सुविधाएँ मिलती हैं। अब वह व्यवस्था के सामने घुटने टेकने पर मजबूर कर दिया जाता है। व्यवस्था द्वारा उसे सुविधाएँ देकर उसका मुँह बंद कर दिया जाता है। इससे पहले विमलेंदु अपनी ईमानदारी के लिए गुंडों द्वारा मरवा दिया जाता है। उसकी आत्मा अरविंद को आगाह करती है कि वह ईमानदार या आदर्शवादी बनने का ढोंग न करें। वह भी विमलेंदु की तरह मारा जाएगा। हमारे समाज में आदर्शवादी, ईमानदार तथा व्यवस्था से पंगा लेने वाले को सिर्फ मौत मिलती है। अच्छा होगा कि तुम जुबान बंद कर चुपचाप नौकरी करो अपने बीवी बच्चों का ख्याल रखो। वरना यूनिवर्सिटी के चेयरमैन की अध्यक्षता में तुम्हारी शोक सभा होगी।

विमलेंदु अरविंद को अपने नाटक के द्रोणाचार्य की याद दिलाता है कि,''जो हाल द्रोणाचार्य का हुआ वही तुम्हारा भी होगा अर्थात तुम भी छल से ही मारे जाओगे।''[९]

प्रिंसिपल बनने के बाद दूसरी बार प्रोफ़ेसर अरविंद को अपने प्रेसिडेंट अर्थात व्यवस्था से टकराने का अवसर मिलता है। कॉलेज की बीस वर्षीय छात्रा अनुराधा कॉलेज के बगीचे में अपने प्रेमी चंदू का इंतजार कर रही थी। चंदू किसी काम से शहर से बाहर गया हुआ था। अनुराधा को अकेली देखकर प्रेसिडेंट का बेटा राजकुमार अनुराधा पर बलात्कार करने की कोशिश करता है। इस बीच प्रिंसिपल अरविंद वहाँ आ जाते हैं। इस दृश्य को देखकर आश्चर्यचकित हो जाते हैं। उन्हें अपनी आँखों पर विश्वास नहीं होता। अनुराधा घर जाकर अपने माता- पिता को घटना की खबर देती

है तथा राजकुमार को कॉलेज से निकलवाने की बात कहती है। उसके पिताजी कहते हैं कि, हम लोग गरीब हैं रिपोर्ट करने पर हमारी बदनामी होगी। उधर प्रेसिडेंट अनुराधा के पिता को पाँच हजार देकर उसकी जुबान बंद कर देता है।

अगले दिन अनुराधा प्रिंसिपल अरविंद से मिलने आती है। वह राजकुमार को रेस्टीकेट करने की विनती करती है। अरविंद पहले तो उसे समझाते हैं कि रेस्टीकेशन के बाद भी वह तुम्हें परेशान करेगा किंतु अनुराधा नहीं मानती। प्रोफेसर अरविंद अनुराधा का साथ देने के लिए तैयार हो जाते हैं। इतने में प्रेसिडेंट का फोन प्रिंसिपल अरविंद के लिए आता है। वह प्रिंसिपल अरविंद को फोन पर अनुराधा का साथ न देने का आदेश देता है। प्रोफेसर अरविंद के न मानने पर वह १५००० रुपयों के गबन के केस में फँसा देने की धमकी देता है। अपने को घिरा हुआ व ठगा हुआ समझकर अरविंद अनुराधा का साथ नहीं देता।

इस तरह अनुराधा वहाँ से चली जाती है। अगले दिन खबर मिलती है कि अनुराधा ने ट्रक के नीचे आकर आत्महत्या कर ली। प्रिंसिपल अरविंद आत्मग्लानि से भर उठता है। विमलेंदु की आत्मा उससे कहती है कि।''उसकी मौत के लिए केवल तुम जिम्मेदार नहीं हो, बल्कि तीन लोग हैं- प्रेसिडेंट, उसका पिता और तुम।''[१०] इससे अरविंद का पश्चाताप कुछ कम होता है।

इस प्रकार प्रिंसिपल आदर्शवादी सिद्धांतवादी तथा ईमानदार प्राध्यापक दो बार व्यवस्था के सामने घुटने टेक देता है। पहले जब, प्रेसिडेंट का बेटा छुरा सामने रखकर नकल करते हुए पकड़ा गया था। दूसरी बार तब जब प्रेसिडेंट का बेटा राजकुमार अनुराधा पर बलात्कार करने की कोशिश करता है। प्रिंसिपल अरविंद प्रमुख गवाह होते हुए भी अनुराधा का साथ नहीं दे पाता। अनुराधा ट्रक के नीचे आकर आत्महत्या कर लेती है।

जब प्रिंसिपल को बार-बार समझौता करना पड़ता है । आत्मग्लानि से भरकर कहता है,''मैं समझौते के फंदे पर पच्चीसों बार अपने को लटकाने वाला..... मैं दूसरों के नकाब उतारने की कोशिश में खुद नंगा हो जाने वाला ....मैं.....मुझ पर थूको।''[११]

निष्कर्ष रूप में यह कहा जा सकता है कि प्रस्तुत नाटक में एक ओर वर्तमान शिक्षण व्यवस्था के खोखलेपन और झूठी समाज सेवा का पर्दाफाश किया गया है । शिक्षण-तंत्र धन एवं जन-बल से प्रतिभा एवं योग्यता को खरीद लेता है। वहीं दूसरी

ओर अपनी आर्थिक व्यवस्था, परिवार तथा मित्रों के दबाव में अरविंद जैसे प्राध्यापक न चाहते हुए भी बार-बार व्यवस्था के समक्ष घुटने टेकने और परिस्थितियों से समझौता करने के लिए मजबूर कर दिए जाते हैं।

एक ओर प्रेसिडेंट जैसे लोग बीसियों शिक्षण संस्थाएँ खोलकर खुलेआम शिक्षण के नाम पर व्यापार कर रहे हैं। सरकार तथा अन्य स्रोतों से आने वाली ग्रांट की धनराशि का उपयोग अपने निजी लाभ के लिए करते हैं। इस पूंजी से अपनी पूंजी को चार-आठ गुना करके वह धन कॉलेज को लौटा कर यह जताने की कोशिश करते हैं कि मानो कॉलेज को अनुदान दे रहे हैं। दूसरी ओर अरविंद जैसे प्राध्यापकों की मजबूरी का लाभ उठा कर उन्हें ब्लैकमेल किया जाता है, कठपुतली की तरह इस्तेमाल किया जाता है।

इस तरह 'एक और द्रोणाचार्य' नाटक के चार प्रमुख उद्देश्य हैं। पहला वर्तमान शिक्षा व्यवस्था का वास्तविक चित्रण। दूसरा वर्तमान शिक्षक/प्रोफेसर की गृहिणियों द्वारा विषम आर्थिक परिस्थितियों में घर चलाने की प्रतिबद्धता को दर्शाना, तीसरा कॉलेज प्रेसिडेंट जैसे संस्था-चालकों के संरक्षण में राजकुमार जैसे खलनायक शिष्यों के निर्माण को रेखांकित करना चौथा छात्रा अनुराधा के माध्यम से स्त्री जीवन की पीड़ा का अंकन करना।

नाटककार ने द्रोणाचार्य को प्रतीक रूप में चित्रित किया है। जिस प्रकार द्रोणाचार्य अपने राजकीय कर्तव्य का पालन करने के लिए व्यवस्था के सामने झुक जाते हैं, वह एकलव्य से कहते हैं कि योग्यता और प्रतिभा से बड़ी चीज व्यवस्था है। व्यवस्था को तोड़ा नहीं जा सकता। यही स्थिति प्रोफेसर अरविंद की भी है। वह दो बार प्रेसिडेंट के बेटे को लेकर व्यवस्था के सामने न चाहते हुए भी हथियार डालने के लिए मजबूर हो जाता है। दरअसल उसके पास इसका कोई दूसरा विकल्प नहीं है।

अतएव, यह कहा जा सकता है कि द्रोणाचार्य हर कालखंड में विवश लाचार ही दिखाई पड़ते हैं। महाभारत काल में राजकीय कर्तव्य के समक्ष जिस प्रकार द्रोणाचार्य ने अपने घुटने टेक दिए, हथियार डाल दिए। ठीक उसी प्रकार प्रोफेसर अरविंद प्रेसिडेंट के समक्ष बार-बार समझौता करने पर मजबूर हो जाता है। कुल मिलाकर एक और द्रोणाचार्य व्यवस्था और व्यक्ति के बीच के द्वंद्व की रचना है।

अंतत: व्यवस्था व्यक्ति पर भारी पड़ जाती है। ऐसे में हमारे समाज को चाहिए कि वह एक ऐसे व्यक्ति का निर्माण करे जो व्यवस्था पर भारी पड़ सकता है, परंतु

निकट भविष्य में इसकी संभावना कम ही दिखाई पड़ती है क्योंकि जब कुछ दिन पूर्व नालंदा विश्वविद्यालय के चांसलर नोबेल पुरस्कार विजेता प्रोफेसर अमर्त्य सेन ने व्यवस्था के विरुद्ध बयान देने का साहस किया तब उन्हें अपनी कुर्सी छोड़नी पड़ी थी।

संदर्भ

१. एक और द्रोणाचार्य, डॉ. शंकर शेष, पृ.२४
२. वही
३. वही
४. वही, पृ.४५
५. वही
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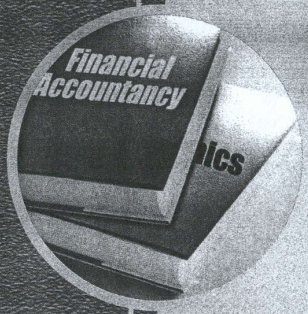

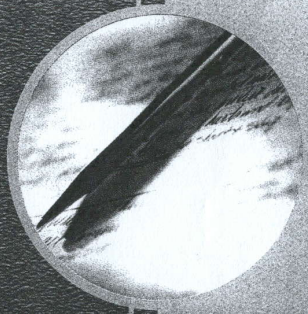

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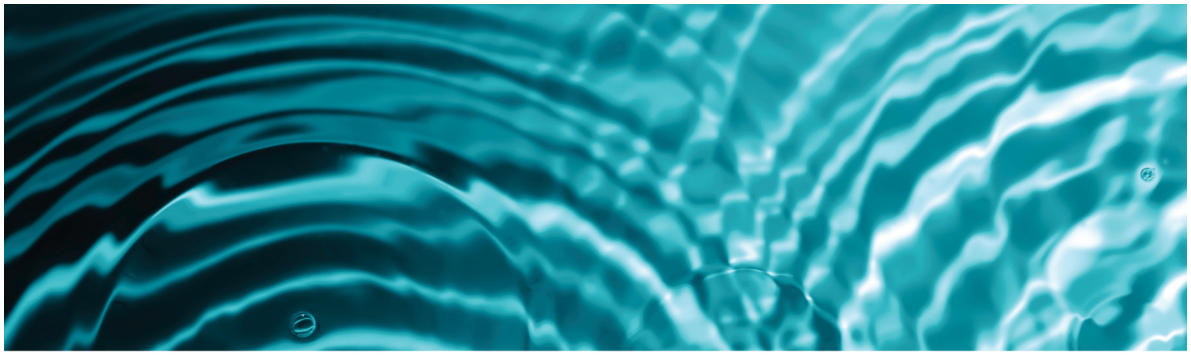

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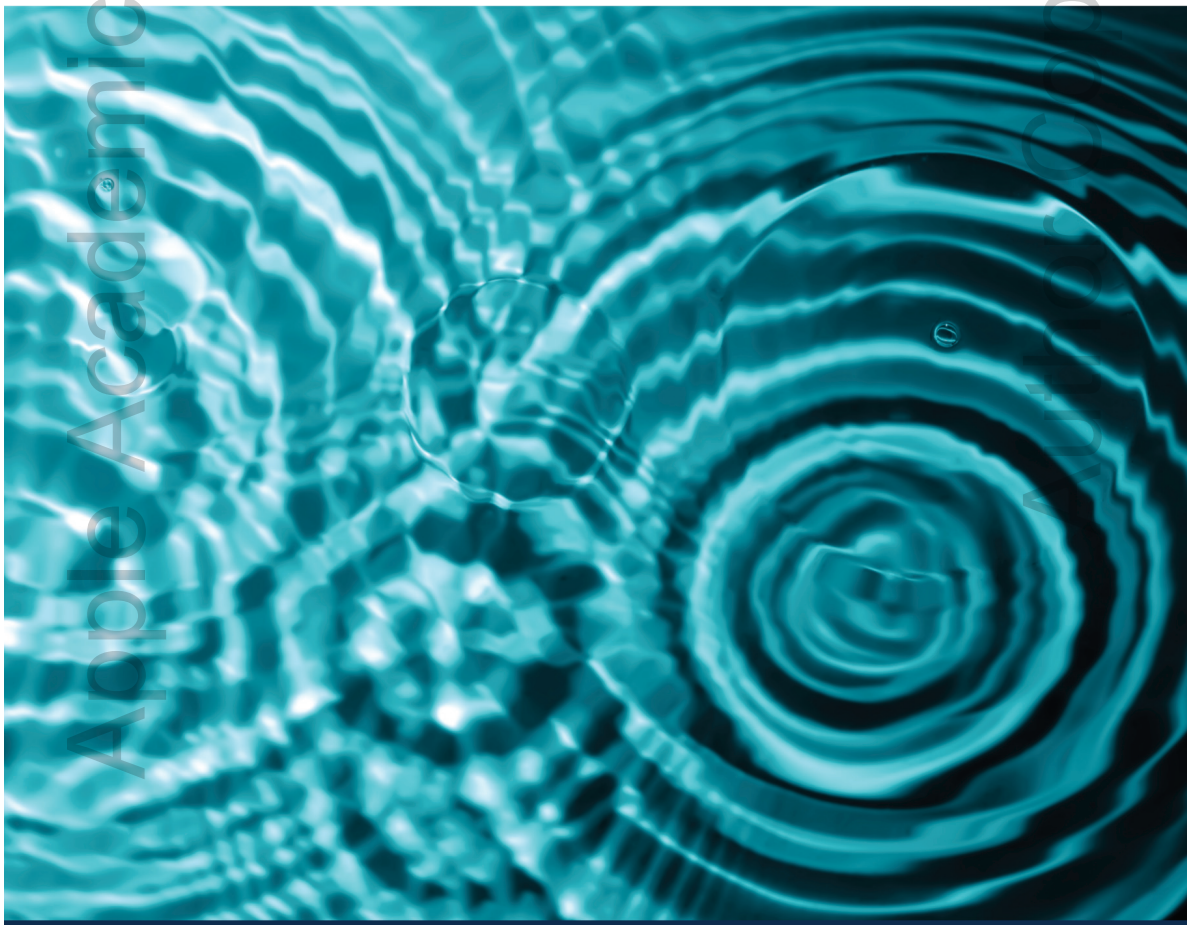

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PREFACE

Nature needs protection from the fast growing chemical pollution. The primary challenge for chemists is to make chemical processes more environmentally benign and sustainable. World has witnessed a tremendous outburst in modifying chemical processes to make them sustainable for making our environment clean and green. One such environmental friendly technique is the use of ultrasound.

Sonochemistry deals with the effect of ultrasonic waves on chemical systems. It has green value because of nonhazardous acoustic radiation and therefore, it is duly recognized as a part of Green Chemistry by synthetic chemists as well as environmentalists. There is no direct interaction of ultrasound with molecular species, but the observed chemical and physical effects of ultrasound are due to the cavitational collapse, which produces drastic conditions of temperature and pressure locally. It induces the formation of various chemical species, which cannot be easily attained under conventional conditions. Sometimes, these species are responsible for driving towards an unusual reactivity in molecular entities.

Exposure to ultrasonic radiation and the resultant sonochemical and/or sonophysical effects have established this technique for driving a particular chemical reaction more efficiently and that too with high yields and selectivity. Sonochemistry utilizes less hazardous starting materials, reagents and solvents. In this process, product selectivity and product yields are increased; in addition, energy consumption is also reduced. This book provides the complete development of sonochemistry starting from introduction, basic concepts of sonochemistry, different types of sonochemical reactions, instrumentation, use of ultrasound in driving particular chemical reactions and its applications in various fields such as polymer synthesis, decontamination of water and waste water, preparation of nanomaterials, food technology, pharmaceutical sciences and so forth.

Apart from this, some fields are also discussed in brief, which do not fall in the actual arena of sonochemistry, but utilize ultrasounds of different frequencies. These are food products and their processing, anaerobic digestion of waste, medical applications such as ultrasonography, sonodynamic

CHAPTER 10

ANAEROBIC DIGESTION

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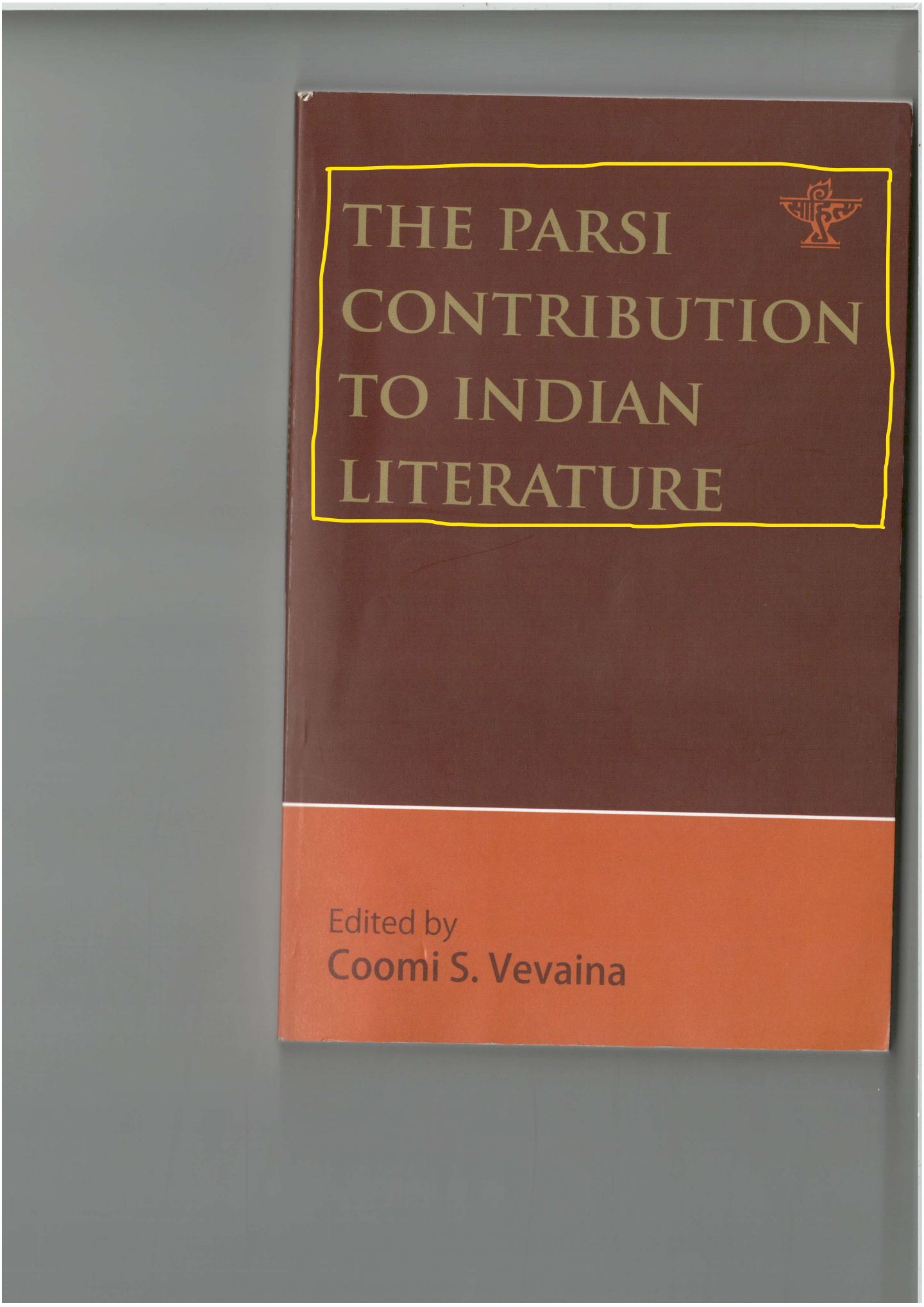
10.1 INTRODUCTION

Wastewater treatment has become a necessity of the day as the world is in cancerous grip of water pollution and is facing a scarcity of potable water in many developing and undeveloped countries. Many techniques are used for the treatment of wastewater, and biological treatment of wastewater is one of these widely used techniques. Excess sludge production is one


THE PARSI
CONTRIBUTION
TO INDIAN
LITERATURE
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Coomi S. Vevaina

The Parsi Contribution to Indian Literature: This book is a compilation of papers presented at the Symposium on The Parsi Contribution to Indian Literature. It is divided into two sections with the first section entitled "In Their Own Words", containing interviews with writers like Adil Jussawala, Keki N. Dauwalla, Thrity Umrigar, Marzban F Shroff and Anosh Irani, and the second, "In Our Words", containing scholarly papers ranging from an overview of Parsi Literature and a visually interesting paper on the way in which literature inspired the archeological excavations in Sanjan, to works of specific writers like Behram Malbari, Dastur Dr. Manekji N. Dhalla, Amal Kiran (K.D. Sethna), Dina Mehta, Gieve Patel, Rohinton Mistry, Cyrus Mistry and Kersi Rustomjee. The explorations are from a wide range of theoretical perspectives with the intention of enabling readers from within the Parsi community to regard themselves from diverse lenses and building bridges of understanding about the Parsis among non-Parsi readers.

Coomi S. Vevaina is an internationally acclaimed critic, writer, teacher trainer and storyteller. Having retired as the Head of the Department of English, University of Mumbai, she is now the Founder Director of *Centre for Connection Education and Management*. She has published 9 books and 58 papers that have appeared in renowned national and international journals and critical anthologies. She has won numerous national and international awards and has been declared as among the ten best Canadian critics in the world by the International Journal of Canadian Studies, Ottawa. Her recent book, *What Children Really Want*, got her recognized by the World Leaders in Education (WLE) as among thirty-five women from across the world who are involved in changing educational paradigms.

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Divine Inspiration in Amal Kiran's *The Adventure of the Apocalypse*

Pearl Pastakia

Introductory Note

I was introduced to Shri K. D. Sethna, poet, philosopher and critic of culture, on my first visit to Sri Aurobindo Ashram, Pondicherry in November 1999. It seemed a fortuitous happening spurred by a senior sadhak asking if we would be paying a visit to Shri K. D. Sethna, who like us, was a Parsee. My mother, who accompanied me then, was overjoyed at the prospect of meeting this venerable personality who was at once a fellow Parsee and a senior disciple and so we set off at once to visit K.D. Sethna, or, as Sri Aurobindo called him, Amal Kiran (Sanskrit for 'Serene Ray'), who was then in his nineties. Amal, having sustained a fracture of the hand, was convalescing in the Ashram Nursing Home on the sea-front. He spoke to us patiently and allowed me to click some pictures of him with my mother. On that visit, we picked up several of his works of literary criticism, but not his poems, since they were not stocked in the Ashram bookshops, then as now.

Some years later, when I scoured the library of St. Xavier's College, Mumbai, which was his and my own Alma

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D. Sethna, poet, philosopher
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Mater, I found an anthology of his poems, 'The Adventure of the Apocalypse', inscribed in the poet's own hand, 'Affectionately to Freddie from Kekoo'. The inscription is dated: '- 16 / 6 / 49 -' and includes an elaborate Preface by the author.

The Preface is significant for being a personal narrative of the way the poems in the anthology came into being and for the light it throws on some of the techniques of poetic creation in general, a subject of abiding curiosity to readers, critics and aspiring writers. The Ashram poet was also a teacher of poetry and regularly discoursed on what makes a poem work.

Addressing a question frequently put to him by interviewers, forty years after the publication of his anthology, K.D. Sethna, speaking in an interview with Valeria and Sudhakar in August 1988, reflected on the qualities of a poet, the connection between poetry and spirituality and the act of literary creation. He said:

> A real poet is one who has the capacity to express himself with intensity of vision, intensity of word and intensity of rhythm. These three intensities in whatever degree are required to make a poem a poem; otherwise it is at best some kind of very efficient verse. But there are various types of poetry, one must admit . . . A true poem can be about anything but in all poetry there is a spiritual force at work; it can work directly and it can work indirectly. Mere belief in God will not do, your every line must move like a god. Then whether you believe in God or do not, it does not matter so far as poetry is concerned. You have to write from some inner source – that is all.

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e. Shroff represented Mumbai at the
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Pearl Pastakia is Head of the Department of English at St Xavier's College (Autonomous), Mumbai. She has published research articles on writers such as K. D. Sethna (Amal Kiran), 'Kavi' Ardeshir Khabardar, Sri Aurobindo, the Mother of Pondicherry and Dasturji Dr Maneckji N. Dhalla. Her Ph. D. thesis, titled 'The Evolution of the Soul in Selected Twentieth Century Autobiographical Writings,' dealt mainly with the personal writings of Dasturji Dhalla, Thomas Merton, Sri Aurobindo and The Mother of Pondicherry and was guided by Dr Coomi S. Vevaina. Her areas of interest include Indian Writing in English and Zoroastrian Studies. She is avidly interested in the writings of the Mother and Sri Aurobindo and has acquaintance with Avesta, the ancient language of the Zoroastrian scriptural texts.

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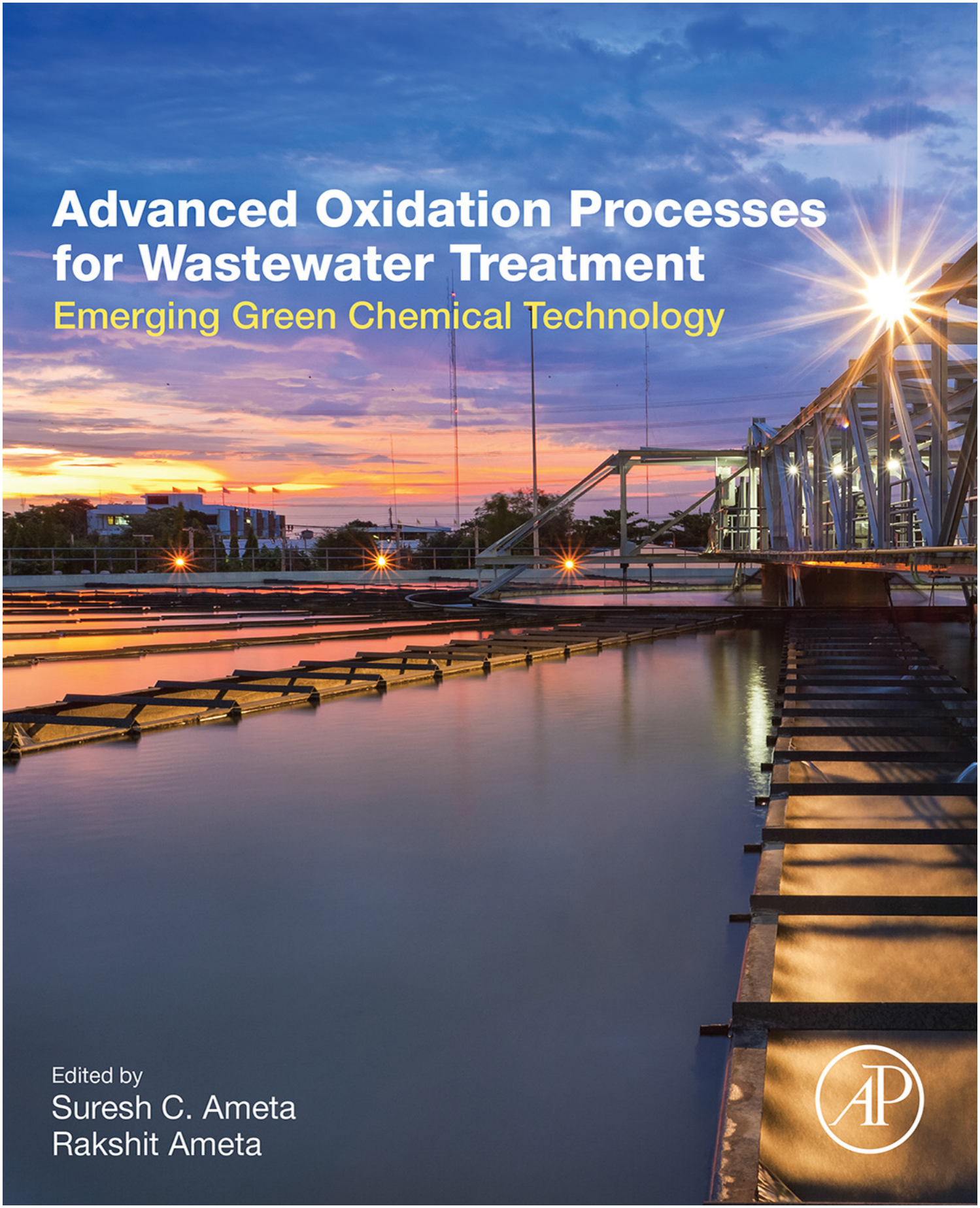
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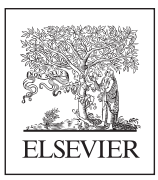

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Fenton and Photo-Fenton Processes

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3.1 INTRODUCTION

Global economic growth is increasing exponentially in the first century of the new millennium, but at the same time, rapid urbanization and industrialization release enormous volumes of wastewater imposing various adverse effects on human health and grading the quality of the environment as a whole. It has been revealed that generation of wastewaters with complex and recalcitrant molecules is increasing day by day. The presence of these organic compounds in water poses a serious threat to public health since most of them are toxic, endocrine disrupting, mutagenic, or potentially carcinogenic to humans, animals. and aquatic life. There is a pressing demand for newer technologies for the complete mineralization of wastewaters.

Several conventional treatment methods are available such as biological, adsorption, chemical treatment, filtration, flocculation, activated charcoal and ion exchange resins for wastewater remediation. It has been frequently observed that pollutants not amenable to biological treatments may also be characterized by high chemical stability and/or by strong difficulty to be completely mineralized. In this context, oxidation processes are preferred to degrade such biorefractory substances present in wastewater. However, pollution load, process limitations, and operating conditions are the key factors to be considered during the selection of the most appropriate oxidation process for the degradation of a particular compound. Apart from high degradation efficiency, direct oxidation processes demand specified operating conditions to degrade the target compounds, which will increase the operation cost of the process.

Advanced Oxidation Processes for Wastewater Treatment
DOI: https://doi.org/10.1016/B978-0-12-810499-6.00003-6

Floral Diversity of Nandur Madhameshwar Wildlife Sanctuary

A Pictorial guide

By
Rajendra D. Shinde

Floral Diversity of Nandur Madhameshwar Wildlife Sanctuary
- A pictorial Guide

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PREFACE

The diverse flora of India has been documented mainly in formal "Floras" ranging from J.D.Hooker's Flora of British India (1875-1897) to district or even taluka-level floras. However, the rapidly growing interest amongst laypeople in the environment and in nature study in the last two to three decades has created a demand for literature which would help a layperson to identify and learn more about the flora of a region; Flowers of Sahyadri by Shrikant Ingalhalikar (2001) was a pioneering and very successful attempt to fill this lacuna for the much-visited mountains of the Sahyadris; Pradip Krishen's Trees of Delhi (2006) and his more recent, Jungle Trees of Central India - a Field Guide for Tree Spotters (2013) are other popular examples; incidentally both the above authors are non-botanists!

A visitor to a wildlife sanctuary is primarily interested in the fauna, in a wetland the primary interest is birds, yet in the intervals when the animals are not visible a secondary interest often arises in identifying the flora, especially flowers or plants with some peculiar morphology. This book is an attempt to help the visitor to Nandur Madhameshwar Wildlife Sanctuary identify and learn some uses of the plants most likely to be encountered and noticed by an amateur visiting the Sanctuary. We hope to stimulate an interest in the diversity and beauty of the flowering plants in a wetland and, thus, promote their appreciation and conservation.

Rajendra Dattatraya Shinde

ACKNOWLEDGEMENT

This book would not have been possible without the help of Late Dr. Marselin R. Almeida and Dr. (Ms.) Saramma Almeida who initiated the project and was involved in the project till its completion.

I thank the Maharashtra Forest Department for financing this book, especially Shri. M.K. Rao, Additional Principal Chief Conservator of Forests (Wildlife West), Borivali, Mumbai; Shri. N. R. Praveen, Conservator of Forests (Wildlife), Nashik, and Shri. Bharat Shinde, Assistant Conservator of Forest, Nandur Madhameshwar Wildlife Sanctuary, Nashik; it was Shri. B. Shinde who pushed me to write this book.

I am thankful to Dr. Rajdeo Singh who took the responsibility of taking photographs in the field as also in the compilation of the book & Ms. Candice Dcosta, who painstakingly edited the original manuscript of my thesis earlier.

I would like to acknowledge the help provided by Mr. V. K. Mohan, Retired IFS office, who was the DFO, Nashik during 1984-88, and Mr. Debi Goenka who accompanied us on field trips and taught me to identify a few common waders.

I am grateful to Dr. Agnelo Menezes, Principal, St. Xavier's College (Autonomous), Mumbai for constant support and encouragement, and to my colleagues in the Blatter Herbarium & Botany Department for helping me in sharing my responsibilities and giving me time to do this work.

And finally to my family who always support me in all my endeavors...

Rajendra Dattatraya Shinde
Mumbai
January 11, 2018.

Disclaimer

INTRODUCTION :

Nandur Madhameshwar Wildlife Sanctuary, also known as 'Mini-Bharatpur' of Maharashtra, is situated at 20°00.780' N and 74°10.4424' E in Niphad tehsil of Nashik district (Map 1). The primary routes to reach this area are from Nashik via, either Sayakheda (35 kms) or Sinnar (55 kms). Niphad railway station on the Central Railway is 12 kms from Nandur Madhameshwar and can be traversed by ST bus. A stone pick-up weir was constructed in 1907-13 across the river Godavari just below the confluence of Kadwa and Godavari rivers at Nandur Madhameshwar; the water level therefore is always fluctuating in Nandur Madhameshwar Lake. This reservoir is surrounded by grape vineyards and fields of sugarcane, onions, jowar, wheat. There are no forests in this area but it is rich in herbaceous flora and aquatic vegetation.

An irrigation reservoir which is known as 'Khangaon thadi' or Nandur Madhameshwar reservoir is situated near Khangaon thadi village, about 2 km away from Nandur Madhameshwar. Due to siltation, the reservoir is gradually becoming a shallow lake and it represents a sort of marshy ecosystem. It has three big islands in the middle and has an abundance of vegetation, fishes, mollusks and insects. Various species of *Cyperus, Typha, Amaranthus, Potamogeton, Ipomoea* and *Eichhornia* which are abundant on the islands provide excellent hiding and roosting places especially for different types of ducks. It is a paradise for many other birds; they feed upon plants and build their nests on them. Recent surveys have recorded 265 species of birds, 7 mammal species and 41 butterfly species in the area (Forest Dept., Nashik Div.). Due to constant efforts of local organizations, Bombay Natural History Society (BNHS), World Wide Fund for Nature-India (WWF-India) and the Forest Department, in 1978, this area was declared as a 'Protected Area' under the Wildlife (Protection) Act 1972 by the Maharashtra Government (Gaz. of Govt. of Maharashtra, 1978) and subsequently was declared as Nandur Madhameshwar Wildlife Sanctuary (Government of Maharashtra, Revenue and Forest Dept. Gazetteer, March 20, 1986, under the sub-sections (1) and (2) of Section 18 of the Wildlife (Protection) Act, 1972 (53 of 1972) (Appendix I page 29). The Nandur Madhameshwar Wildlife Sanctuary spans an area of 100.12 sq. km.

Two canals emanate from the Nandur Madhameshwar reservoir - the Godavari Left Bank Canal and the Godavari Right Bank Canal - with a total capacity of 7,763 m.c.ft. The reservoir irrigates a cultivable area of 88,000 Acres, which falls in Niphad and Yeola tehsils of Nashik district and Kopergaon tehsil of Ahmednagar district. The Godavari Right Bank Canal is approximately 111 km in length and irrigates a cultivable area of 1,36,380 Acres, falling in Niphad and Sinnar tehsils of Nashik district and Kopergaon and Shrirampur tehsils of Ahmednagar districts.

Historical importance:

In the middle of the riverbed in between Khangaon thadi and Nandur Madhameshwar village, standing on a small rocky islet, is a 250 years old temple of 'Madhyameshwara' from which the village has derived it's the second half of its name. The lamp pillar near the temple bears an inscription dated 1738 with the name of an ascetic.

Agricultural importance : Niphad tehsil has an area of 1,05,228 ha, of which 90,631 ha is

Argemone mexicana L.

Family : Papavaraceae
Common Name : Pivala-Dhotra
Habitat : Common weed in waste land and in cultivated fields
Location : Khangaon thadi, Manjargaon
Fl. & Fr. : Throughout the year
Description : Annual, erect, prickly herb. Leaves are radical or cauline, variegated white, spiny on margins and veins, sessile. Flowers are yellow, axillary, solitary.
Uses : Entire plant is anti-fungal and also possess anti-leprotic activity.

Asparagus racemosus Willd.

Family : Liliaceae
Common Name : Shatavari
Habitat : Common along the hedges
Location : Khangaon thadi
Fl. & Fr. : June to October
Description : Shrubs with tuberous fascicled roots. Cladodes slender, glabrous. Flowers white in raceme.
Uses : Bark of plant show antibacterial activity and roots are used as galactogogue.

Azadirachta indica (L.) A. Juss.

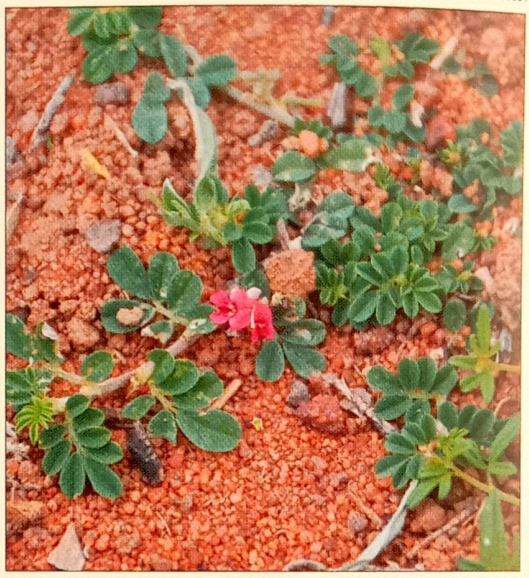
Family : Meliaceae
Common Name : Kadunimb
Habitat : Commonly cultivated along the canal and road sides.
Location : Khangaon thadi, Manjargaon
Fl. & Fr. : March to June
Description : Trees with leaves crowded near end of branches. Leaflets ovate-lanceolate. Flowers white, in axillary panicles.
Uses : Flowers and Leaves are antibacterial and used as an analgesic.

Impatiens balsamina L.

Family : Balsaminaceae
Common Name : Terda
Habitat : Rare in horticultural land.
Location : Khangaon thadi
Fl. & Fr. : July to August
Description : Annual herbs with alternate, elliptic, acute leaves. Flowers pink, axillary, fascicled; lateral sepals ovate with short spur.
Uses : Plant possess anti-fungal and anti-cancer activity.

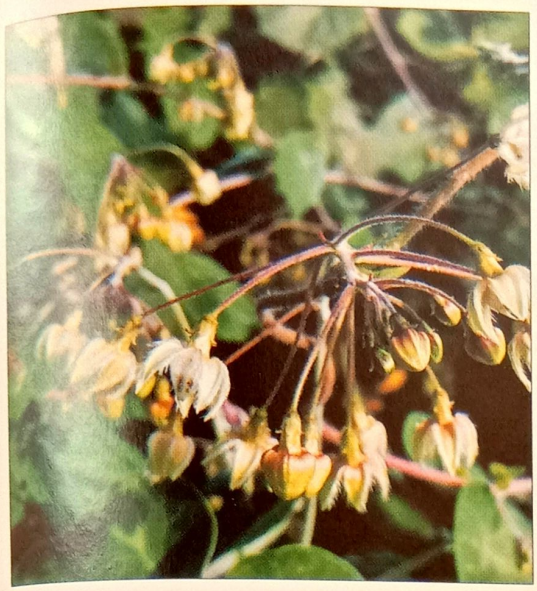
Indigofera cordifolia Heyne ex Roth

Family : Fabaceae
Common Name : Bechka
Habitat : Common along the river bed
Location : Khangaon thadi
Fl. & Fr. : Throughout the year
Description : Herbs, prostrate, pilose. Leaves are ovate, acute, cordate, pilose on both surfaces. Flowers are red, 4-6 in number, in condensed racemes, tomentose.
Uses : Seeds are aphrodisiac and used as bitter tonic.
Photo : Dr. Mayur Nandikar



Indigofera linifolia (L.f.) Retz.

Family : Fabaceae
Common Name : Lal Godhadi
Habitat : Common along the river bed.
Location : Khangaon thadi, Manjargaon
Fl. & Fr. : July to December
Description : Herbs, prostrate, much branched, pubescent. Leaves simple, linear, acute, pubescent on both sides. Flowers bright red, in sessile or shortly peduncled axillary racemes.
Uses : Seed oil is anti-microbial and nutritive tonic.



Pergularia daemia (Forssk.) Chiov

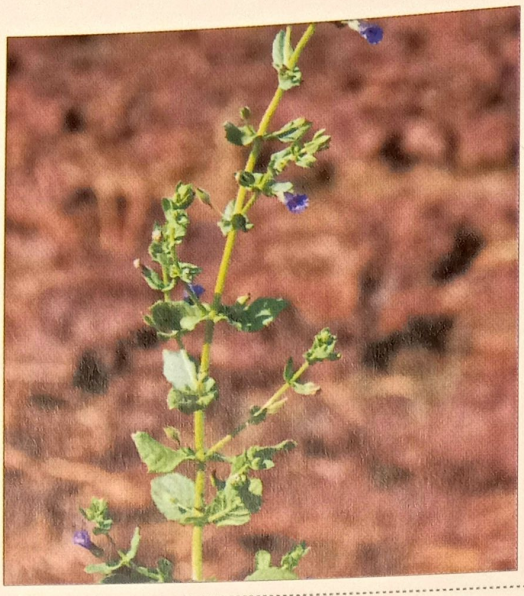
Family : Asclepidaceae
Common Name : Utarn
Habitat : Common along the hedges
Location : Khangaon thadi, Manjargaon, Tarul-Khedale
Fl. & Fr. : March to December
Description : Herbs, twining, with milky sap. Leaves suborbicular with cordate base. Flowers in cymes, pubescent.
Uses : Leaf juice is emetic and used against snake bite.

Persicaria glabra (Willd.) M. Gomez

Family : Polygonaceae
Common Name : Sheral
Habitat : Common along the river banks
Location : Madhameshwar, Manjargaon
Fl. & Fr. : October to March
Description : Herbs, stem thick, reddish after drying. Leaves lanceolate, acute or acuminate at apex, entire, glabrous. Flowers pink, in terminal racemes.
Uses : Leaves are used in colic pain and as febrifuge.

Phyla nodiflora (L.) Greene

Family : Verbenaceae
Common Name : Jalpimpli
Habitat : Common in dried cultivated lands
Location : Khangaon thadi
Fl. & Fr. : Throughout the year
Description : Herbs, prostrate, with woody root stocks, rooting at the nodes, pubescent. Leaves oblanceolate-obovate, subsessile to sessile. Flowers purple or white, solitary, axillary or in spikes.
Uses : Infusion of leaves and stalks are given to women after delivery and also plant is used for joint pain.

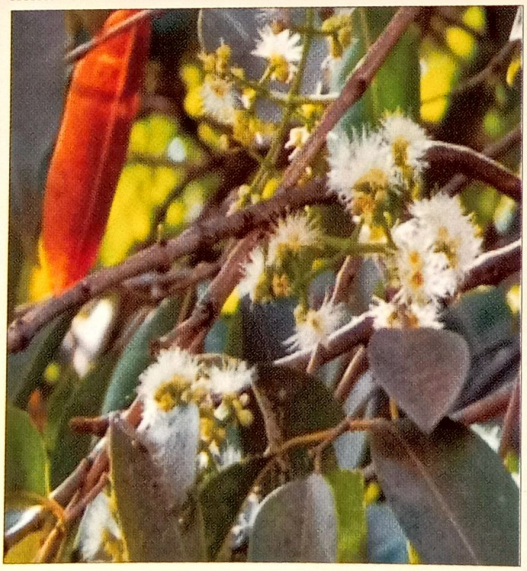


Stemodia viscosa Roxb.

Family : Scrophulariaceae
Common Name : Satmodi
Habitat : Common along the river banks and in moist places
Location : Khangaon thadi, Manjargaon, Madhameshwar
Fl. & Fr. : November to January
Description : Herbs, erect, aromatic; stem and branches are viscidly pubescent. Leaves sessile, oblong, acute, serrate, pubescent. Flowers purple, solitary, axillary or in terminal racemes.
Uses : Infusion of plant is used as demulcent.

Striga angustifolia (D. Don) Saldanha

Family : Scrophulariaceae
Habitat : Rare in grasslands
Location : Madhameshwar
Fl. & Fr. : July to October
Description : Much branched stout herb. Leaves linear, sessile, scabrous. Flowers sessile or shortly pedicellate, in long, erect spikes or racemes.
Uses : Plant is used in diabetes



Syzygium cumini (L.) Skeels

Family : Myrtaceae
Common Name : Jambhul
Habitat : Common; cultivated in the farms and gardens for its edible fruits
Location : Khangaon thadi
Fl. & Fr. : March to May
Description : Trees, Leaves lanceolate, elliptic-oblong or broadly ovate-elliptic. Flowers dirty white, in panicled cymes.
Uses : Fruit is used in diarrhoea and dysentery.

9 789353 001681

A red Coloured mat of *Azolla pinnata* R. Br., an aquatic free-floating fern on the water surface and *Typha angustifolia* L. in the background.

Dr Rajendra D. Shinde
M.Sc., Ph.D.

Dr Rajendra D. Shinde is the Head, Department of Botany & the Director, Blatter Herbarium at St. Xavier's College (Autonomous), Mumbai.

He is the member of the "Plant Biodiversity Expert Committee", Maharashtra State Biodiversity Board since 2017. He has served the St. Xavier's College in the capacity of Vice-Principal from 2010 to 2017. He is Elected Fellow of the Indian Association Angiosperm Taxonomy, Life Member of Society of Ethnobotany, Association of Plant Taxonomy, Indian Botanical Society, Bombay Natural History Society, Alumni of the Fulbright-Nehru Programme (2012), Rotary Foundation-Rotary International: GSE programme (2000), Nominated Member of Tree Authority - Thane Municipal Corporation (2014-2017). Angiosperm Taxonomist by specialization, he has been teaching Botany at St. Xavier's College, Mumbai since 1991. He has also served as a Curator of the Blatter Herbarium from 1983 to 1991. During the year 2003-2004, Dr Shinde had an opportunity to serve as a senior lecturer at the Faculty of Natural Sciences, University of Guyana, Georgetown, Guyana (South America). Systematic and ecological studies on the Nandur Madhmeshwar, Nashik District, Maharashtra (1988), Arboreal Flora of Greater Bombay (1993), Tree Census of Greater Bombay (1998), Tree Census of Thane Municipal Corporation (2002), Digitized Inventory of Medicinal Plants Resources of Maharashtra (2009-2013) are some of the major projects completed by him along with five minor research projects from various funding agencies.

Besides several research papers in reputed and peer-reviewed journals, he has authored a book entitled "Ethno medicinal plants of Raigad District, Maharashtra (2016). He is a well-known research guide in the field of Angiosperm Taxonomy and Ethnobotany and got 4 PhD awarded under his guidance so far.

During his Master's study at St. Xavier's College, along with Late Dr. M.R. Almeida, he had visited Nandur Madhameshwar during 1984-1988 regularly to study the flora of the area. He updated this work in the year 2012-2015. He has reported 536 plant species from the Nandur Madhameshwar Wildlife Sanctuary during this study. This book is the outcome of this study.

A Study of Retention and Motivational Practices in Banks with Special Reference to Mumbai City

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1 INTRODUCTION

1.1 INTRODUCTION

A bank is a financial institution and a financial intermediary that plays a role in accepting deposits and channelises those deposits into lending activities, either directly or through capital markets is called a bank. A bank brings together customers that have capital deficits to customers who are flooded with capital surpluses.

A bank creates credit. It does so by lending money to a borrower, and thereby creates a corresponding deposit on the bank's balance sheet. As a financial institution its Lending activities can be performed either directly or indirectly through capital markets. Due to their significance in the existing financial system and influence on national economies, banks remain highly regulated in most countries. Most nations have institutionalised a system known as Fractional Reserve Banking under which banks hold liquid assets equal to only a portion of their current liabilities. In addition to other regulations intended to ensure liquidity, banks are generally subject to minimum capital requirements based on an international set of capital standards, known as the Basel Accords.

Banking as is understood today evolved in the 14th century in the rich cities of Renaissance Italy but in many ways was a continuation of ideas and concepts of credit and lending which already existed in the ancient world.

A bank is a financial institution licensed as a receiver of deposits. There are two types of banks: Commercial/Retail Banks and Investment Banks. In most countries, banks are regulated by the National Government or Central Bank.

Definition of Banking

Kent defines banking as "an organisation whose principal operations are concerned with the accumulation of the temporarily idle money of the general public for the purpose of advancing to others for expenditures."

Sayres defines banking as "Ordinary banking business consists of changing cash for bank deposits for cash; transferring bank deposits from one person or corporation (one 'depositor') to another; giving bank deposits in exchange for bills of exchange, government bonds, the secured or unsecured promises of businessmen to repay, etc."

Under the Banking Regulation Act, 1949, banking accepting involves money for the purpose of lending or investment of deposits money from the public which is repayable on demand or otherwise and can be withdrawn by cheque, draft, order or otherwise.

Public Sector Banks

Public Sector Banks (PSBs) are banks where the government is a majority stake (i.e. more than 50%) is held by the government. The shares of these banks are listed on stock exchanges. There are a total of 27 PSBs in India [19 Nationalised banks + 6 State Bank group (SBI + 5 associates) +IDBI+BMB].

In 2011 IDBI – Industrial Development Bank of India and in 2014 BMB – Bharatiya Mahila Bank were nationalised with a minimum capital of ₹ 500 cr.

Private Sector Banks

Private Banking renders services similar to PSBs but is more personalised as against a mass market retail banking, investment and other financial services provided by banks to high-net-worth individuals with high levels of income or invest sizable assets. It is usually guided by dedicated bank advisers. It does not refer to a private bank, which is a non-incorporated banking institution.

Employee Retention refers to the ability of an organisation to retain its employees. Motivation is the perceived needs of the employees, satisfaction of contribution of employees' performance and productivity.

Employee Retention refers to the various policies and practices which let the employees stick to an organisation for a longer period

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पाठ्य-पुस्तक

(F. Y. B. A.)

संपादिका

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भूमिका

किसी कक्षा विशेष के लिए पाठ्य-पुस्तक के रूप में संकलन तैयार करते समय जिन बातों पर विशेष ध्यान दिया जाना चाहिए वे हैं विद्यार्थियों की भाषा विषयक जानकारी तथा उनका बौद्धिक स्वास्थ्य। इस संकलन को तैयार करते समय भाषा तथा पाठ्य सामग्री विषयक ये दो बातें मेरे लिए सबसे महत्वपूर्ण थीं। प्रथम वर्ष कला (F.Y.B.A.) में प्रवेश पानेवाले विद्यार्थी भिन्न-भिन्न बोर्ड से परीक्षाएँ उत्तीर्ण करके आते हैं। इनका हिन्दी भाषा के ज्ञान का स्तर भी भिन्न होता है। कुछ विद्यार्थी आठवीं कक्षा के बाद तो कुछ दसवीं कक्षा के बाद हिंदी पढ़ना छोड़ चुके होते हैं। कुछ विद्यार्थियों को हिंदी बहुत मुश्किल लगती है जबकि कुछ विद्यार्थियों का हिन्दी भाषा तथा साहित्य का ज्ञान प्रशंसनीय होता है। यही बात हिन्दी भाषा के व्याकरण तथा वर्तनी की उनकी समझ पर भी लागू होती है। इस सबके बावजूद बौद्धिक तथा भावनात्मक रूप में ये सभी विद्यार्थी बहुत पास-पास होते हैं। इसलिए संकलन तैयार करते समय अनेक-अनेक विचारों को ध्यान में रखना होता है ताकि हर विद्यार्थी पाठ्य-पुस्तक से जुड़ाव अनुभव कर सके।

'शशि-भारती' को आप एक साहित्यिक यात्रा कह सकते हैं, एक कथा कह सकते हैं। मेरा प्रयत्न यह रहा है कि इस पाठ्य-पुस्तक के माध्यम से हम प्राध्यापक अपने विद्यार्थियों को हिन्दी साहित्य के विकास की कथा के साथ-साथ साहित्य के माध्यम से भारत की कथा भी सुना सकें। यह पुस्तक केवल मन रंजन (मनोरंजन) न करे, आत्मरंजन और आत्ममंथन का साधन भी बने। केवल परीक्षा में पास होना भर लक्ष्य ना हो वरन जीवन जीने की राह ढूँढने में भी सहायक बने। धीर-गंभीर उपदेशात्मक रचनाओं से मैंने बचने का प्रयत्न किया है। मैं मानती हूँ कि अट्ठारह-उन्नीस वर्ष के विद्यार्थी से यह कहना कि संसार माया है, मिथ्या है इसे त्याग दो-उचित नहीं है। इस उम्र में वे जिस उत्साह, उमंग और ऊर्जा से भरे हुए रहते हैं, उसे केवल सही दिशा की ओर अग्रसर कर देना पर्याप्त है। विद्यार्थी के मन और मस्तिष्क का विकास हो यही कामना है। विद्यार्थियों की सहायता हेतु पाठ्य-पुस्तक के अंत में रचनाकारों का परिचय दिया गया है। आशा है विद्यार्थी लाभान्वित होंगे।

अब ये संकलन आपके सुपुर्द है इस विश्वास के साथ कि हम आप हिंदी से प्यार करें और प्यार बाँट सकें।

आशा नैथानी दायमा

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1. पुष्प की अभिलाषा

■ माखनलाल चतुर्वेदी

चाह नहीं है, मैं सुर-बाला के गहनों में गूँथा जाऊँ,
चाह नहीं, प्रेमी-माला में बिध, प्यारी को ललचाऊँ,
चाह नहीं, सम्राटों के शव पर हे हरि! डाला जाऊँ,
चाह नहीं, देवों के सिर पर चढ़ूँ, भाग्य पर इठलाऊँ,

मुझे तोड़ लेना बनमाली!
उस पथ पर देना तुम फेंक।

मातृभूमि पर शीश चढ़ाने,
जिस पथ जावें वीर अनेक।

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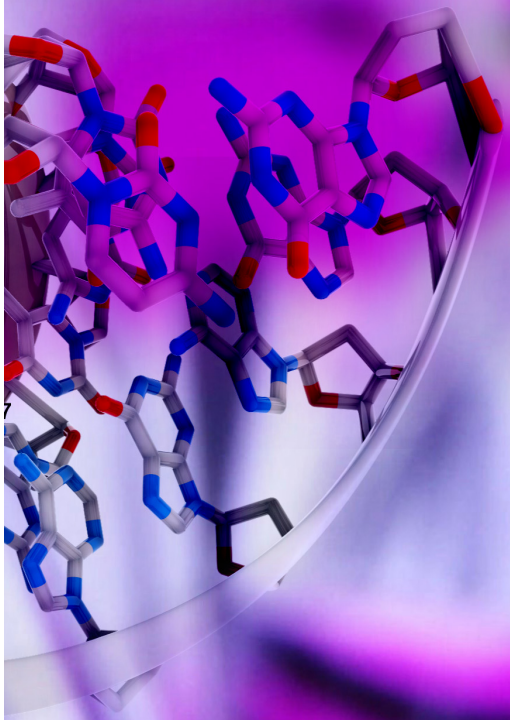

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FOREWORD

The sixth volume of Topics in Anti-Cancer Research presents some exciting contributions in frontier areas of anti-cancer research. These include the role of microtubules for the treatment of various cancers, novel chemoimmunotherapy drug combinations & methods in clinical studies/trial and current studies in targeting polyunsaturated fatty acids (PUFAs) in the treatment of colorectal cancer. Natural and synthetic chalcones and their derivatives that have shown potent anticancer activity against a number of cancer cell lines and murine tumor models are discussed. The discovery of selective small-molecule hLDH-A inhibitors and LDH-based approaches in the progress of anticancer therapy are also presented. Recent advances in microRNA-based cancer therapeutics for the treatment of cancer are presented. The role of inflammation in chemotherapy-induced neuromuscular effects and the side effects and recent relevant patents for beneficial approaches to improve heart failure cases due to inflammation, mitochondria and energy metabolism in cancer cachexia are also covered. It is hoped that the present volume will be found useful by a large number of scientists working in this field.

The editors are thankful to the authors for their excellent contributions and to the reviewers for their in -depth comprehensive comments for the improvement of chapters. We are also grateful to Mr. Mahmood Alam, Mrs. Rafia Rehan and other colleagues for their support and assistance in the finalization of this volume.

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INTRODUCTION

Topics in Anti-Cancer Research covers important advances on both experimental (preclinical) and clinical cancer research in drug development. The book series offers readers an insight into current and future therapeutic approaches for the prevention of different types of cancers, synthesizing new anti-cancer agents, new patented compounds, targets and agents for cancer therapy as well as recent molecular and gene therapy research.

The comprehensive range of themes covered in each volume will be beneficial to clinicians, immunologists, and R&D experts looking for new anti-cancer targets and patents for the treatment of neoplasms, as well as varied approaches for cancer therapy.

The topics covered in the sixth volume of this series include:

- The role of microtubules for the cure of various untreated cancers
- Novel chemoimmunotherapeutic drug combinations & methods in clinical studies/trials
- Targeting polyunsaturated fatty acids (PUFAs) in the treatment of colorectal cancer
- Anti-cancer activity of natural and synthetic chalcones and their derivatives
- Recent advances in microRNA-based cancer therapeutics
- Treatment of heart failure due to inflammation, mitochondria and energy metabolism in cancer cachexia
- Regulation/inhibition of human lactate dehydrogenase A for discovering anti-cancer drugs

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CHAPTER 1

Targeting Polyunsaturated Fatty Acid Metabolism in Colorectal Cancer Therapy: A Review of Recent Patents

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Abstract: In the recent years, fatty acids (FAs) have been acknowledged not only as building materials for lipid membranes and carbon source for β-oxidation, but also as important signaling molecules. In this field, polyunsaturated fatty acids (PUFAs) have received special attention as modulators of inflammation. The enzymes that process PUFAs into bioactive metabolites (cyclooxygenases, lipoxygenases) have already been targeted by pharmaceutical agents. Given the fact that intense synthesis of FAs is a metabolic hallmark of cancer, it is expected that FAs play an important role in cancer development, progression and invasion, and could be targeted by modern therapies. In this chapter, we will discuss the possible use of FAs and drugs affecting their metabolism against colorectal cancer (CRC), which is strongly associated with environmental factors such as high-fat, high caloric diet and obesity. We will cover the role of n-3 PUFAs as dietary supplements in primary prevention of CRC based on the results obtained from clinical trials, and elaborate on the latest patents designed to improve the bioavailability of PUFAs concentrates as nutritional treatments for patients with CRC. We will also discuss the enzymes processing PUFAs and their role in tumorigenesis with focus on their potential as markers for "molecular staging" (fatty acid synthases and elongases) and targets in therapy (cyclooxygenase 2 and lipoxygenase 5). Finally, we will examine new drug formulations (e.g. liposomes) and their utility in CRC therapy. The chapter is based on the review of literature (PubMed Database) and patent documents.

Keywords: Adjuvant therapy, chemotherapy, colorectal cancer, cyclooxygenase, dietary supplementation, docosahexaenoic acid, eicosapentaenoic acid, fatty acids, gastrointestinal cancer, inflammation, lipoxygenase, liposomes, nutritional treatment, polyunsaturated fatty acids, prevention, patents.

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1. INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in women and third in men, responsible for 600,000 deaths annually worldwide [1 - 3]. It is the fourth cause of oncological deaths, which creates a substantial global burden [4]. Up to 50% of CRC risk is lifestyle-related - most prominent risk factors include obesity, sedentary behavior, alcohol consumption, tobacco smoking, high-meat / high-calorie intake, as well as fat-rich and fiber-deficient diet [5]. All of these disturb the metabolic balance and add to CRC development. A cause-effect relation has been proven for alcohol (which promotes folate deficiency and thus leads to DNA instability and carcinogenesis) and tobacco smoking (which spreads carcinogens from cigarettes to colorectal mucosa, stimulating carcinogenesis) [5]. In turn, dietary habits and sedentary lifestyle not only cause obesity but also lead to the development of metabolic syndrome highlighted by a range of abnormalities encompassing impaired glucose tolerance, elevated blood pressure and dyslipidemia. These metabolic disorders tip the cytokine balance toward chronic low-grade inflammation and further disturb the levels of adipokines e.g. adiponectin and leptin, and insulin growth factors which all affect cellular proliferation, adhesion and migration [6 - 8]. Moreover, unbalanced diet can directly promote carcinogenesis by modifying the intestinal microbiome and making alterations in the complexity of the colorectal mucosa - for details see [6].

Alterations in lifestyle patterns through higher intake of fish and fish oils, dietary fiber, vitamin D and calcium, regular use of aspirin and habitual physical exercise modulate the course of CRC, especially at the initial stage of its development, and improve the quality of life of patients [5]. The protective role of fish and fish oils is mainly attributed to the high content of polyunsaturated fatty acids (PUFAs). The fact that aspirin also acts on the metabolism of PUFAs further suggests that these fatty acids may play a significant role in CRC development and possible prevention.

PUFAs are organic acids comprising of a carbohydrate chain with more than one double (C=C) bond in their structure. Long-chain PUFAs are divided into n-6 PUFAs (first double bond at C6, counting from the methyl C) and n-3 PUFAs (first unsaturated bond at C3). The main representatives of these groups are linoleic acid (LA, 18:2) for n-6 PUFAs and α-linolenic acid (ALA, 18:3) for n-3 PUFAs, together called essential fatty acids (FAs). The term “essential” emphasizes their importance in maintaining the optimal health of humans and other animals, as they cannot be synthesized de novo but have to be supplemented in the diet. These FAs provide the carbon chain necessary for the synthesis of longer FAs: n-6 arachidonic acid (AA, 20:4), and n-3 eicosapentaenoic acid (EPA, 19:5) and docosahexaenoic acid (DHA, 22:6) in the reactions catalyzed by

elongases and desaturases. In humans, the efficacy of transforming ALA to longer n-3 PUFAs is low and personally variable [9] and thus its derivatives should also be supplemented in diet. Animal-derived products (meat, eggs, dairy) are the most common source of LA and its derivative AA, whereas fish, particularly salmon, provides mainly n-3 PUFAs.

This chapter will briefly describe the fundamental knowledge of PUFAs and their metabolism. A detailed section is devoted to reports from the *in vitro* and *in vivo* studies investigating links between PUFAs and CRC. The main body covers various ways in which PUFAs could be utilized to prevent or treat cancer, especially CRC, based on the already established patents and promising reports from the literature.

The review is based on literature search conducted in the following databases: PubMed (for original papers and reviews), ClinicalTrials.gov, EU Clinical Trials Register and UMIM (for clinical trials), and WIPO (for pertaining to patents). The keywords used to search for patents included: adjuvant therapy, chemotherapy, colorectal cancer, dietary supplementation, docosahexaenoic acid, eicosapentaenoic acid, endocannabinoids, fish oil, liposomes, polyunsaturated fatty acids and resolvins. The literature was searched in relation to relevant patents. Non-English articles were not included in the review. All patents and clinical trials mentioned in this paper are summarized in Tables **1** and **2**, respectively.

2. PUFAS AND THEIR METABOLITES

PUFAs are important elements of cellular lipid membranes released into circulation by phospholipase A2. By undergoing various enzymatic and non-enzymatic pathways, PUFAs are converted into biologically active lipid metabolites and mediators (Fig. **1**). The most prominent enzymes participating in the formation of bioactive metabolites of n-3 and n-6 PUFAs include:

- Cyclooxygenases (COXs) that produce prostaglandins (PGs), thromboxanes (TXs) and prostacyclins;
- Lipoxygenases (LOXs) which process AA into lipoxins (LXs) and leukotrienes (LTx), and n-3 PUFA into protectins, marensins and resolvins;
- Cytochrome 450 (Cyp 450) which converts PUFAs into hydroxyeicosatetraenoic acids (HETEs).

CHAPTER 2

Microtubules as Anti-Cancer Drug Targets

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Abstract: In developmental biology, all cellular events are suitably synchronized to ensure proper growth and development of any multicellular organism. A healthy adult tissue is often characterized by stem cells that can undergo orchestrated cell division and differentiation. Disruption of these events often leads to cancer resulting from the accretion or accumulation of the genetic and epigenetic changes that occur at the somatic as well as the germ line levels. In the recent years, significant progress has been made in the early detection, treatment and prevention of cancer. Targeted cancer therapies include the use of apoptosis inducing drugs and drugs that target microtubules among others. Over the past few years, drugs that inhibit microtubule dynamics have been successfully used as anticancer drugs. They can either be microtubule stabilizers (Vincristine, Vinblastine, Colchicine etc.) or microtubule destabilizers (Paclitaxel, Docetaxel, Epithilones, Taccalonolides etc.). Recently, new classes of compounds have been identified that interfere with cell growth and proliferation as a consequence of binding to tubulin αβ- dimers. Natural compounds like Curcumin have shown to inhibit tubulin activity. Whereas some antimitotic agents like Aurora A/B, Pentoxifylline, benzimidazole derivatives, combrestatin, polymeric nanoparticles etc. have been reported to show significant effect in the treating several types of cancer which were previously deemed untreatable. The following chapter acknowledges the presence of these anti-tumor compounds and how they target microtubules and further aid in the treatment of various cancers afflicting human beings.

Keywords: Antimitotic agents, Aurora A, Apoptosis, Cancer, Combretastatin analogs, Colchicine, Curcumin, Docetaxel, Epothilones, Microtubules, Microtubule polymerizers, Microtubule depolymerizers, Paclitaxel, Pentoxifylline, Taccalonolides, Taxanes, Tubulin, Vinca alkaloids, Vinblastine, Indexing words: Microtubules, Anti-cancer drug targets, Microtubule stabilizers, Taxanes, Epothilones, Taccalonolides, Microtubule destabilizers, Vinca alkaloids, Colchicine, Halichondrin B, Dolostatin 10, Aurora A, Curcumin, Pentoxifylline, Combretastatin, Benzimidazole derivatives, Casein K2 peptide inhibitor, Nanoparticles.

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1. INTRODUCTION

1.1. Cancer

Cancer is the second leading cause of death in the world with the first position being conferred to cardiovascular diseases. The word cancer finds its origin from the Greek word *Karkinos* which was the term used by the Greek physician, Hippocrates (460-370 B.C) to describe carcinoma tumours. Within the developing embryo, events such as stem cell divisions, their fate determination, proliferation of cells and their migration followed by apoptosis need to be orchestrated. In an adult, the constant turnover of cells as well as their optimal functioning is ensured by the division and differentiation of the stem cells that are present in small numbers in the healthy tissues [1]. Cancer is thought to be the disruption of this critical organisation resulting from the accretion or accumulation of the genetic and epigenetic changes that occur at the somatic as well as the germ line levels [2]. This causes uncontrolled proliferation of normal cells and subsequently leads to the formation of cancerous cells which proceed to grow, proliferate and re-divide giving rise to abnormal cells instead of undergoing apoptosis. These cells have several features in common with stem cells. The observation of these similarities led to the advent of two alternative hypotheses, one stating that the stem cells might themselves be the targets of the mutations that transform them while the other suggesting that the dedifferentiation of those cells that are transformed and terminally differentiated gives rise to cancer stem cells (CSCs), thereby manifesting the disease [3] Cells of different types of cancer migrate via the blood circulation or lymph vessels to the other regions of the body and begin to grow in that target region. This phenomenon is termed as “metastasis”. These cells are incapable of DNA repair and hence can be considered malignant (cancerous). However, some tumors do not possess the capacity to grow and migrate to the other parts of the body and are, therefore, categorized as benign (non-cancerous) [4].

Cancer is a multistage disease however; work carried out on cancer recognizes a link between chronic inflammation and cancer with Virchow (1863) hypothesising that cancer originates at the sites of chronic inflammation [4]. More advanced studies on cancer suggest that the inflammatory cells are actually involved in the promotion of cancer progression [5]. Most of the malignancies have been observed to be initiated by chronic inflammation or tissue injury, which can be associated to known parasitic, viral or bacterial infections [6].

Worldwide estimates about 15% of the malignancies (1.2 million/year) attributed to chronic infections instances of which include liver cancer caused due to Hepatitis B and C infection, cervical cancer caused due to human papilloma virus

and gastric cancer resulting from *Helicobacter pylori (H. pylori)* infection. Individuals susceptible to an increased risk of cancer exhibit increased polymorphisms in the genes encoding pro-inflammatory cytokines. Population-based studies have established that when tissues are chronically inflamed, the susceptibility to cancer increases and also the risk of many cancers reduces significantly as a consequence of long- term use of NSAIDs, thereby demonstrating the vital role of inflammation in the pathogenesis of cancer [7].

1.2. Hallmarks of Cancer

Advances in cancer research has gained new insights and it is thought to be a disease that involves dynamic changes in the genome; the basis of which has been built on the discovery of mutations that lead to the production of oncogenes and tumour suppressor genes. ***Oncogenes*** are the genes which have gained dominance over the function. They drive the normal cells towards unrestrained growth and develop into cancer cells. Proto-oncogenes are the normal genes of the cell that regulate the frequency of cell division as well as the extent of its differentiation. Oncogenes arise when mutations occur in the proto-oncogenes. ***Tumor suppressor genes*** are the normal genes that are involved in regulating cell division, DNA repair and signalling of apoptosis. Tumor suppressor genes experience recessive loss of function. Any dysfunction in a tumor suppressor gene results in an uncontrollable growth of cells thereby causing cancer [8].

Cancer cells possess impaired regulatory circuits that are responsible for normal cell proliferation and maintenance of homeostasis. More than 100 distinct types of cancer exist with many subtypes of tumors being found within specific organs. The vast catalog of cancer genotypes is thought to be manifested due to six of the crucial alterations in the physiology of cells which eventually lead to a malignant growth. The six alterations seen are as follows:

1. Loss of sensitivity to growth-inhibitory signals: Tissue homeostasis is maintained when cells respond to anti-proliferative signals during G1 phase. However cancerous cells become insensitive to such signals due to the disruption of retinoblastoma proteins which helps in filtering anti proliferative signals.
2. Evasion from apoptosis: Cancerous cells grow in number not only because they become proliferative but also because they tend to evade cell death mechanisms.
3. Self- sufficiency in growth signals: Once a normal cell gets transformed into a cancerous cell, their dependency on exogenous stimulatory growth factor is scaled down. This is due to the fact that the oncogenes tend to mimic the growth signals in one form or the other.

CHAPTER 3

Effects of Inflammation, Mitochondria and Energy Metabolism in the Heart due to Cancer

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Abstract: Cancer cachexia is a paraneoplastic syndrome characterised by significant skeletal muscle wasting and cardiac atrophy. It occurs in 50% of patients with cancer and approximately 20% of cancer deaths are attributed to cachexia. Heart failure due to cancer cachexia is suggested to contribute to the high mortality rate and currently there is limited therapeutic intervention. The relationship between inflammation and energy metabolism as well as mitochondrial dysfunction in the heart in the context of cancer cachexia will be discussed. This chapter provides an understanding of potential, novel molecular mechanisms that could be of interest when considering therapeutic interventions for heart failure due to cancer cachexia. In summary, several interrelated molecular effects should be considered in cancer-induced cachexia in cardiomyocytes. TNF-α induced mitochondrial dysfunction may be important for the generation of ROS. IL-6 may induce an autophagic/mitophagic response as a result of downregulation of mitochondrial STAT3 due to mTOR suppression. An imbalance in mitochondrial dynamics may contribute to insulin-resistance and atrophy. Decreased expression of ANT1 may contribute to MPTP dysfunction and an altered energetic profile from adult to fetal metabolism. The effects of ANT1 expression in cardiac muscle during cancer cachexia is worth investigating in mouse models as discussed with reference to an ANT1 patent in this chapter. Furthermore, patents that are relevant for therapeutic strategies to ameliorate heart failure in cancer cachexia have also been discussed. Patents addressing interventions that could be applied to cancer cachexia-induced cardiac atrophy include: sodium selenite treatment, inhibitory agents of NADPH oxidase such as phycobilin, an AMPK inhibitor, modulation of mitochondrial biogenesis and modulation of mTOR. Understanding the underlying molecular mechanisms of mitochondrial dysfunction in cardiomyocytes during cancer cachexia-induced cardiac atrophy may reveal novel molecular targets for therapeutic intervention.

Keywords: Cancer, cancer cachexia, cardiac atrophy, cardiomyocyte, energy metabolism, heart failure, inflammation, inflammatory cytokines, mitochondria,

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mitochondrial dynamics, mitochondrial dysfunction, mitophagy, muscle wasting.

1. INTRODUCTION

Cancer cachexia is a multifaceted paraneoplastic syndrome occurring in approximately 50% of patients with cancer [1, 2]. It is a significant contributor to cancer morbidity and mortality, with approximately 20% of cancer deaths due to this syndrome [1, 2]. The disease is defined as progressive skeletal muscle wasting with anorexia, increased catabolic drive and functional impairment that is not effectively reversed with nutritional supplementation [3]. Heart failure and cardiac atrophy have also been reported in cancer cachexia [4]. Recent investigations suggest that cardiac atrophy may contribute to the high mortality rates in patients with cancer induced cachexia [5, 6]. The pathogenic mechanisms of cancer cachexia-induced cardiac failure are not well established.

Current research on cancer cachexia in cardiac tissue has relied on the development of animal and cell culture models due to the reduced availability and accessibility of human clinical samples [4]. Given the significant metabolic derangement in patients with cancer-induced cachexia, mitochondrial dysfunction may play a role in the pathogenesis of cancer cachexia-induced heart failure [7 - 9]. This chapter will focus on how known pathological mechanisms and previously identified key molecules relate to mitochondrial dysfunction in the heart in the context of cancer cachexia.

2. INFLAMMATORY CYTOKINES AND MITOCHONDRIAL DYSFUNCTION IN CARDIAC TISSUE

2.1. Tumour Necrosis Factor-α

Elevated inflammatory cytokines may facilitate heart failure in cancer cachexia by affecting cardiomyocyte mitochondrial function. Tumour Necrosis Factor (TNF)-α induced mitochondrial dysfunction in cardiomyocytes involves the generation of increased reactive oxygen species (ROS) [10, 11]. ROS may either induce, or result from, mitochondrial dysfunction. Therefore, investigating the source of ROS in cardiomyocytes may determine if mitochondrial dysfunction is a primary or secondary process in the pathogenesis of cancer cachexia in the heart. The main mitochondrial source of ROS in the heart is the electron transport chain (ETC), whilst non-mitochondrial sources in the heart include NADPH oxidases (Nox) and uncoupled nitric oxide synthases (NOS) [12]. TNF-α administered to a rat cardiomyocyte cell culture model demonstrated that the ETC was the major source of ROS [10]. Furthermore, in a ventricular pacing-induced canine model of

Congestive Heart Failure (CHF), TNF-α inhibition partially and completely restored cardiomyocyte mitochondrial complex III and ATP synthase activities respectively and ameliorated oxidative stress (Table **1**) [13]. Thus, demonstrating that ETC is a source of ROS. In another ventricular pacing-induced canine model of CHF, blocking the function of complex I in the ETC in cardiomyocytes increased ROS production 2.8-fold. Interestingly, complex I enzymatic activity was decreased in the context of heart failure, possibly contributing to uncoupling and ROS production in mitochondria [14]. Further evidence of an ETC source has also been observed in a fibrosarcoma cell culture model, where TNF-α primarily produced ROS at the ubiquinone site [15]. These studies suggest a potential role for TNF-α- induced alterations in mitochondrial function in cardiomyocytes. Future therapeutic strategies, such as sodium selenite treatment, could target mitochondrial dysfunction to ameliorate cancer cachexia-induced cardiac atrophy [16].

Table 1. Summary of the Effects of Inflammatory Cytokines on Mitochondria in the Heart.

Cytokine	Model	Effect of the Cytokine Studied	Mechanism or Signalling Pathway	Reference
TNF-α	Canine model of pacing-induced CHF	Mitochondrial production of ROS	Complex III and ATP synthase dysfunction	Moe *et al*., 2004 [13]
	Adult human cardiomyocyte cell culture	Activation of NF-kβ	NADPH oxidase production of ROS	Moe *et al*., 2014 [17]
	Adult male Sprague-Dawley rats	Decreased ANT protein levels Altered membrane permeability transition pore opening in mitochondria	Increased ROS Unknown - hypothesised to be due to down regulation of ANT1	Mariappan *et al*., 2007 [19]
	Neonatal Wilstar rat ventricular cell culture	ROS mediated mitochondrial DNA damage	Sphingomyelin-ceramide pathway	Suematsu *et al*., 2003 [10]
IL-6	Simulated ischemia/reperfusion in neonatal Sprague-Dawley rat ventricular cell culture	Increase inner mitochondrial membrane polarisation and increase mitochondrial Ca^{2+} loading	PI3-kinase/Akt pathway	Smart *et al*., 2006 [32]

In addition to the ETC, there are other non-mitochondrial sources of ROS in the heart including Nox and NOS [12]. There is emerging evidence for TNF-α-induced ROS generation from NADPH oxidase in cardiomyocytes [17] and TNF-

CHAPTER 4

Chalcone and Their Derivatives as Anticancer Agents

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Abstract: Cancer has eventually stepped into the molecular insights focussing on the development of new generation of anticancer drugs especially of natural origin and its analogues with less or no toxicity issues and targeting specific molecular signalling pathways. In various therapeutic areas, numerous natural products and their derivatives have been effectively used to treat many human diseases or disorders. Chalcones, as metabolic precursors of some flavonoids and isoflavonoids have a structure of open chain flavonoids (1,3-diaryl-2-propen-1-ones) present in fruits and vegetables, possessing a broad range of biological activities including cancer chemotherapeutic and chemopreventive property. The anticancer properties of chalcones have been improved by substituting aryl rings (e.g. methoxy substitution on both aryl rings A and B) and introducing heterocyclic moieties. Hybridization with other pharmacologically important moieties (benzodiazepines, benzothiazoles, imidazolones etc.) by taking the help of SAR (structure-activity relationship) studies with much ease in preparation and oral administration ultimately has made chalcone a safe therapeutic agent. Some clinical trials revealed that these compounds did not cause toxicity and are present in plasma at optimum concentrations. Nowaday's several chalcones are also used in cosmetic formulations and in food additives which could further be utilized for its chemopreventive potential. This book chapter briefly summarizes the demanding efforts made in the development of novel anticancer chalcones recorded in recent literatures with focussed cancer targets as well as presents an outline of the patents published in recent decades.

Keywords: Angiogenesis, antiproliferative, apoptosis, cancer, cell cycle arrest, cell line, chalcone, chalcone derivatives, chemoprevention, cytotoxicity, heterocyclic chalcone derivatives, IC_{50}, metastasis, NFκB, p53, p21, p23, TRIAL, tumor.

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1. INTRODUCTION

Chalcones are phytomolecules belonging to the largest group of secondary metabolites of plant system with chemical structure of 1, 3-diphenyl-2-prope-e-1-ones, in which the two aromatic rings are linked by three carbon α, β-unsaturated carbonyl system (Fig. **1**). The name was derived from "*chalcos*" meaning bronze due to its variant colour and it was given by Kostanecki and Tambor [1]. These compounds have a conjugated system where *p*-electron systems are delocalized with conjugated double bonds on both the benzene rings [2]. Chalcones due to their Michael acceptor features and small structure, easily bind with different cellular metabolites resulting in profound molecular and cellular effect ultimately exhibiting a broad range of biological activities [3]. Chalcones in general have lower redox potential due to enone (alkene-ketone) system and therefore, it prefers more electron transfer reactions. They are assumed to be intermediate metabolites in the synthesis of flavonoids and isoflavonoids that serve mainly for the defense system in the plants and thus protecting them from ROS (Reactive Oxygen Species) and consequently minimizing molecular and environmental injury. Functionally, it serves to regulate cholesterol levels, maintaining blood glucose levels, decrease the blood pressure, remove joint and muscle pain, help in sleep, improves immune system, liver and kidney functions, and enhance vision, skin beauty, hair growth and memory [4].

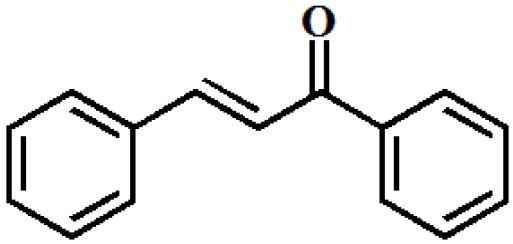

Fig. (1). Basic chalcone structure.

2. CONJUGATES AND DERIVATIVES OF CHALCONES

Chalcone has been widely used in organic synthesis to establish highly enantio-selective Michael adducts. The asymmetric catalytic conjugate adding a stabilized carbanion nucleophile to α, β-unsaturated carbonyl compounds shows one of the most essential carbon-carbon bond forming reactions in organic chemistry because the adducts are interesting intermediates for further optimization, such as amino-carbonyls, pyrrolidines and amino-alkanes. Many chalcone derivatives have also been prepared due to their convenient synthesis [3].

Madhavi *et al*. (2017) studied the synthesis of chalcones incorporating quinazoline derivatives as anticancer agents [5].

Bhale *et al*., (2017) worked on the synthesis of protracted conjugated indolyl chalcones as the strong antioxidant, anti-inflammatory and anti-breast cancer agents [6]. Cai *et al*. (2017) studied the analogues of xanthones-chalcones and bis-chalcones as α-glucosidase inhibitors and anti-diabetes candidates [7]. Hawash and collaborators worked on the synthesis and bioactivity of novel pyrazolic chalcone derivatives as novel hepatocellular carcinoma therapeutics [8]. Ramaiah *et al*., (2011) studied Chalcone-imidazolone conjugates and they found that these synthesized conjugates trigger DNA damage in the cells and show apoptosis [9]. Kamal *et al*., (2015) studied about phenstatin/isocombretastatin-chalcone conjugates as effective tubulin polymerization inhibitors and mitochondrial apoptotic inducers [10]. Similarly, Khan (2009) published a patent on certain novel chalcones derivatives (in particular boronic chalcone derivatives) wherein he claimed that they possess anti-proliferative activity against cancer cells at micro molar concentrations. The invention provides the design and synthesis of novel boronic chalcone derivatives, and pharmaceutical compositions of chalcones derivatives. The invention also reveals the high activity and less toxicity of numerous compounds against breast cancer cell lines compared to normal MCF12A cells [11].

In glioblastoma cell lines, Indole chalcone has been recognized as a possible anticancer agent as it decreases the multiplication of cells under *in vitro* conditions. It was revealed that the indole chalcone battle for the binding site with colchicine and induces the inhibition of tubulin polymerization. Moreover, it distorted microtubule formation and triggered G2/M phase arrest and apoptosis. The molecule also worked as the dual inhibitor of Pgp and BCRP in glioblastoma cell line [12]. Chalcones are reported for both cancer chemotherapeutic action as well as for its chemopreventive mechanism as it possesses ability to inhibit carcinogenesis due to various modes like by increasing reduced glutathione levels and maintaining the optimum redox level [13].

TRAIL (Tumor necrosis factor related apoptosis inducing ligand) indicates programmed cell death specific to cancers and without any toxic effect to normal cells. TRAIL in association with the death receptor DR4 and/or DR5 mediates programmed cell death [14, 15]. However, decrease in the expression of pro-apoptotic proteins, TRAIL-R1 and TRAIL-R2 (death receptors) with concurrent upsurge in the level of anti-apoptotic proteins in tumor cells mediates TRAIL-resistance [16]. Szliszka *et al*. (2010) reported that the TRAIL-induced programmed cell death and cytotoxicity enhanced in prostate cancer cells by chalcones and dihydrochalcones such as phloretin. Their results show the

CHAPTER 5

Regulation/Inhibition of Human Lactate Dehydrogenase A: An Innovative and Potential Approach for Anti-Cancer Drugs Development

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Abstract: Human lactate dehydrogenase (*h*LDH-A), a glycolytic enzyme responsible for the conversion of pyruvate to lactate coupled with oxidation of NADH to NAD^+, plays a crucial role in the promotion of glycolysis in invasive tumor cells. *h*LDH-A has been considered a vital therapeutic target for invasive cancers therefore, *h*LDH-A inhibition reflects a valuable attempt in the development of innovative anticancer strategies. Reagents that regulate or inhibit *h*LDH-A enzyme/ gene can play a role in the prevention and treatment of various cancers and related diseases. In fact, selective inhibition of *h*LDH-A using small molecules holds potential prospects for the treatment of cancer. Consequently, significant progress has been made in the discovery of small-molecules, the selective inhibitors of *h*LDH-A displaying remarkable inhibitory potency. The LDH-based approaches in the development of anticancer therapy and treatment of related diseases are worthwhile because of the existence of LDH enzyme at the end of glycolytic pathway. In this book chapter, 59 review and research articles, and 15 patents filed on LDH and its application are discussed. Latest contributions in regulation/inhibition of the LDH-A enzyme by various agents are summarized in this book chapter.

Keywords: Aerobic glycolysis, anaerobic glycolysis, anti-inflammatory activity, anti-proliferative activity, cancer cell metabolism, cancer cell proliferation, epileptic treatment, FDG-PET, FRET, glycolytic pathway, gossypol, human lactate dehydrogenase A, human lactate dehydrogenase B, isostere of pyruvate, metabolic switch, mitochondrial dysfunction, NADH/NAD^+, nanosensor, *N*-hydroxy-indole, pyruvate dehydrogenase complex, selective *h*LDH5 inhibitors, tumor glycolysis, warburg effect.

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1. INTRODUCTION

Cancer is one major cause among the leading causes of morbidity and mortality worldwide. According to the World Health Organization (WHO) approximately 14 million new cases of cancers and 8.2 million cancer related deaths were reported in 2012 worldwide and among them, most common causes of cancer death are cancers of lung (1.59 million deaths), liver (745 000 deaths), stomach (723 000 deaths), colorectal (694 000 deaths), breast (521 000 deaths) and oesophageal cancer (400 000 deaths) [1]. This data reflect the serious threats of cancer posed to human health, and the development of promising anticancer agents is, therefore, urgently required. WHO launched the global action plan in 2013, for the prevention, control and treatment of non-communicable diseases during 2013-2020 by aiming to reduce premature mortality from cancers. Common conventional approaches that are clinically used for the treatment of cancers, including surgery, chemo- and radiation therapy have some limitations due to serious side effects [2]. Various research studies confirm that cancer is a complex process and many enzymes including glycolytic enzymes are involved in initiation, maintenance and survival of various human cancers and some of them are thus considered as innovative targets for the development of anticancer agents [3]. Significant inhibition as well as reduction of enzyme activity involved in cancer by means of small molecules or other agents is a current and significant approach for drug development. Great efforts have been dedicated to design and develop 'drug-like' small molecules by following target-, structure- and fragment-based approaches for selective enzyme inhibition for the treatment of cancers [4].

2. CANCER CELL METABOLISM

The metabolic properties of cancer cells differ significantly from those of the normal cells. Unlike normal cells, most cancer cells rely on the enhanced rate of glycolysis that tends to ferment glucose into lactate, even under aerobic conditions. In fact, cancer cells are abnormally dependent on aerobic glycolysis for energy production at higher rate for maintenance of cancers [5]. It is hard to discuss the cancer cell metabolism without first mentioning the German scientist "Otto Warburg" who made a striking discovery in the 1920's. For the first time, he observed that the cancer cells hold the metabolic switch from oxidative phosphorylation (OXPHOS) towards aerobic glycolysis (Warburg effect) and thus, established a link between cancer and the peculiar glucose metabolism in cancer cells [6]. Since then "Warburg effect" has been validated in various human tumors and the parallel increase in enhanced glucose uptake has been exploited clinically for the diagnosis, staging, and monitoring of various cancers, including nonHodgkins lymphoma (NHL) by using fluorodeoxyglucose positron emission tomography (FDG-PET). It is a useful and sensitive modality for assessing

disease activity in thyroid lymphoma and in cancer metastasis. In this technique, the biologically active molecule, an analogue of glucose i.e. fluorodeoxyglucose (FDG), is used for PET where the concentration of FDG tracer indicates metabolic activity of the tissue that corresponds to the regional glucose uptake [7]. Besides tumor imaging, Warburg effect can be exploited for drug designing to treat human cancers. Initially, Warburg hypothesized that the metabolic alteration specific to cancer cells is caused by a mitochondrial defect where complete oxidation of glucose is lost; however, it was later proven that this metabolic alteration is from oncogene-directed metabolic reprogramming, not from mitochondrial dysfunction [8 - 10]. The unique characteristic of tumor glycolysis of being highly functional is accompanied by high glucose consumption due to lower efficiency in energy production that ensures an adequate and rapid energy supply and biosynthetic intermediates for rapidly growing cancer cells [10 - 12]. In essence, cancer cells are hungrier for nutrients than normal cells are; thus, tumor glycolysis provides selective advantages to tumor cells for survival and proliferation. Succinctly, cancer is a metabolic disease and can be targeted by the following two facts (i) to produce enough energy to survive when supplies and waste disposal are limited, and (ii) to distract abundant metabolic intermediates to the biosynthetic pathways supporting cell proliferation. Recently, keen research interest in tumor glycolysis has emerged due to the strong metabolic dependencies of cancer cells. Despite various key factors (enzymes and transporters) that are intricate, tumor glycolysis is thus considered a promising target [10, 12].

3. GLYCOLYSIS AND LDHA

Glycolysis is a metabolic process, which comprises ten successive steps catalyzed by specific enzymes in the cytoplasm of the cells. At the end of glycolysis, two pyruvate molecules are formed by the catabolism of one glucose molecule with concurrent generation of two ATP molecules and two NADH (Nicotinamide Adenine Reduced Dinucleotide) molecules. Glycolysis can take place in both conditions; i) in the presence of oxygen i.e. aerobic condition and, ii) in the absence of oxygen i.e. anaerobic condition [13]. Although, in both the situations, the final products viz. two molecules of pyruvate, two molecules of ATP and two molecules of NADH are the same but depending upon the presence or absence of oxygen, further pyruvate can follow two different pathways. In aerobic (normoxia) condition, two molecules of pyruvate are transported into mitochondrial matrix where these molecules are decarboxylated and then enter into Krebs cycle (TCA; tricarboxylic acid) cycle to produce 36 molecules of ATP, carbon dioxide and water by oxidative phosphorylation (Fig. **1A**). In normal cells under normoxia, glycolysis and oxidative phosphorylation are tightly coupled processes. In contrast, in an anaerobic (hypoxia) condition pyruvate is red-

CHAPTER 6

Cancer Chemo-Immunotherapeutics

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Abstract: Cancer chemo-immunotherapeutics has evolved with a strategic slogan - 'marrying chemotherapy with immunotherapy' - in order to optimize the chance for cure. The ultimate goal is to execute a 'two hit' impact, able on the one hand to mount a robust anti-tumour immune response, and on the other hand, selectively eradicate tumour growth and progression. Tremendous progress has been, and being, made in this regard by testing various 'chemotherapy-immunotherapy' drug combinations in the clinic, and also implementing multiple pharmacological and biological interventions against fundamental regulatory pathways involved in tumour development, progression, and tumour immune escape mechanisms. This chapter discusses the current 'chemotherapy-immunotherapy' combinations in clinical studies/trials, as well as the pharmacological manipulation of host-tumour cell interactions mapping the road ahead to a novel trend/concept of 'two hit' chemo-immunotherapeutics. At the end, we also discuss the patents issued and recent patent applications stating the novel chemo-immunotherapy methods with diverse interventional combinations, some of which produce synergistic anti-tumour effects, to treat multiple advanced cancers.

Keywords: ARG, Cancer, Chemotherapy, Chemo-immunotherapy, Cancer vaccines, CIK cells, CTLA4, Cytokine, FOLFOX, GVAX, IDO, Immune suppression, Immuno-oncology, Kinase inhibition, mAbs, mTOR, MAPK, PKA, R-CHOP, TroVax®.

1. INTRODUCTION

Cancer chemo-immunotherapeutics implements treatment regimens that both maximize tumour regression and the anti-tumour immune response for the long

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term clinical benefit of cancer patients [1]. Although cancer chemotherapy has historically been considered as immunosuppressive, emerging evidence indicates that certain chemotherapies can augment tumour immunity through multiple mechanisms including induction of immunogenic cell death and by disrupting strategies that tumours use to evade immune recognition [2 - 4]. This dual role, cytotoxicity and immune activation, from chemotherapy has prompted the scientific community to call for a radical but strategic shift in the way tumours are treated in order to achieve better clinical outcomes [1]. To this regard, cancer chemo-immunotherapeutics has evolved with a strategic slogan - 'marrying chemotherapy with immunotherapy' - in order to optimize the chance for cure [5, 6]. The ultimate goal is to execute a 'two hit' impact, able on the one hand to mount a robust anti-tumour immune response, and on the other hand, selectively eradicate tumour growth and progression. Tremendous progress has been, and being, made in this regard by implementing multiple chemotherapy-immunotherapy drug combinations with complimentary mechanisms of action to attain additive or synergistic anti-tumour effects [7, 8]. Apart from this, the complex interactions between host and tumour cells within the tumour microenvironment may lead to 'tumour-associated immune suppression', which is characterized by diverse mechanisms of oncogenic signaling pathways that play critical roles in tumour initiation, progression, and immunoescape [9]. Emerging data indicate that small-molecule based therapeutic interventions against such signaling pathways may have the potential to provide a 'two-hit' chemo-immunotherapeutic opportunity: direct killing of tumour cells, and the rescuing of endogenous anti-tumour immunity [10 - 12]. The purpose of this chapter is to discuss the clinical significance of current chemo- and immuno-therapy drug combinations, as well as highlight the 'two hit' chemo-immunotherapeutic potential of targeting the oncogenic signaling pathways that play crucial roles in tumour growth and progression, and in tumour-associated immune suppression. Moreover, we also discuss patents issued and recent patent applications demonstrating novel chemo-immunotherapeutic methods/formulations for the treatment of cancer.

2. CURRENT CHEMO-IMMUNOTHERAPEUTIC DRUG COMBINATIONS IN CLINICAL STUDIES

In recent decades, a general trend of harnessing endogenous anti-tumour immunity by modifying the diverse mechanisms of immunosuppressive tumour immune microenvironment has provided the knowledge and techniques to develop novel immunotherapeutic approaches for the treatment of cancer [7]. These include:

a. Antibodies, such as monoclonal antibody drugs (mAbs) and the recent immune checkpoint-modulating antibodies;
b. Vaccines, such as tumour cell-based autologous vaccines and dendritic cell (DC)-based vaccines; and
c. Immunostimulatory cytokines, and cytokine-induced killer (CIK) cells.

Several combinations of these immunotherapeutics with traditional chemotherapy are in various phases of clinical trials (Table **1**). In addition, superior clinical benefits of chemotherapy-immunotherapy combinations have also been convincingly demonstrated in the settings of large randomized trials.

Table 1. Summary of Currently Ongoing Clinical Trials Involving Cancer Chemo-Immunotherapy.

Chemo-Immunotherapy	Target of the Listed Antibody	Type of Cancer	Phase	Reference (NCT ID)
Chemotherapy-mAbs Combinations				
Doxorubicin, vincristine, cytarabine, etoposide, cyclophosphamide, methotrexate, leucovorin, filgrastim, epratuzumab	CD22	Acute lymphoblastic leukemia	Phase I/II	NCT00098839
Bendamustine, lenalidomide, rituximab	CD20	Chronic lymphocytic leukemia; Small lymphocytic lymphoma	Phase II	NCT01754857
Cyclophosphamide, fludarabine, ofatumumab	CD20	B-cell lymphoid leukemia	Phase II	NCT01762202
Bendamustine + ofatumumab	CD20	Mantle cell lymphoma	Phase II	NCT01437709
Carboplatin, paclitaxel, oregovomab	CA125	Ovarian neoplasms	Phase II	NCT01616303
Cisplatin, docetaxel, cetuximab	EGF receptor	Lung cancer	Phase II	NCT01059188
Fludarabine, cyclophosphamide, ofatumumab	CD20	Chronic lymphocytic leukemia; Small lymphocytic lymphoma	Phase II	NCT01145209
Paclitaxel, lapatinib, trastuzumab	HER2/neu	Breast carcinoma	Phase II	NCT01891357
Cyclophosphamide, fludarabine, rituximab	CD20	Multiple leukemias and lymphomas	Phase III	NCT02048813
CHOP chemotherapy (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone) plus G-CSF, combined with alemtuzumab	CD52	T-cell lymphoma	Phase III	NCT00646854
Fludarabine, rituximab	CD20	Chronic lymphocytic leukemia	Phase III	NCT00513747

CHAPTER 7

Recent Advances and Challenges in microRNA-Based Cancer Therapeutics

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Abstract: Despite significant advancements in understanding the cancer-associated signaling cascades, effective treatment strategies remain scarce. This intricacy of cancer enigma highlights a pressing need to develop novel therapeutics. The seminal discovery of microRNAs (miRNAs), a class of natural RNA-interfering agents, provides a new hope for accomplishing this task. Bolstered by a novel mode of action, the ability to function as tiny master regulators of cellular processes, ease of administration and sufficient uptake along with apparent lack of toxicity in normal tissues give miRNAs an extra edge and make them an ideal candidate for emerging therapeutic developments. Genome-wide investigations have shown more than half of the human miRNA genes being located on genomic regions or at fragile sites associated with cancer, unveiling the substantial significance of these small RNAs. Very soon after the discovery of the first miRNA, miRNA-based therapeutics has entered clinical trials and has shown fascinating results in preclinical development. This rapid progress through the discovery pipeline into clinical development imitates the significance of miRNAs as critical regulators in human diseases, and holds the pledge of yielding a novel class of therapeutics that could signify an attractive addition to the existing drug pipeline of Big Pharma. In this chapter, we will give an overview of the recent miRNA-based therapeutic approaches (patents: EP3110951, WO2017005771, EP3126496, EP3106168, WO2017005773, US9399773, EP2217248 and US9469854), and will discuss current translational challenges and further potential developments. These patents describe the potential of different miRNAs inhibitors/mimics for treating various types of cancers, these miRNAs include miR-34 mimic to treat hematologic malignancy/solid tumors; miR-409-5p, miR-379 and miR-154 inhibitors to treat prostate cancer and drug resistant lung cancer; miR-548z, miR-624-5p, let-7i-3p, miR-885-5p, miR-449b-3p to treat hepatoblastoma cancer; pre-miR-302 (an miRNA precursor) for cancer reversion; miR-21, miR-125a-5p, miR-191, miR-210, miR-222, miR-378, miR-423-3p, miR-638 inhibitors to treat hepatocellular carcinoma (HCC); hsa-miR-4510, hsa-miR-548aa, hsa-miR- 548v and hsa-miR-37-b-3p mimics to treat HCC; sorafenib- miR- 34-mimic/ miR-215 mimic combination therapy for treating liver cancer and miR-21-3p mimic for treating liver diseases. The outcome of these patents may hopefully provide exciting opportunities and deeper

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insights into novel anti-cancer paradigms. Compared to conventional drug therapies, miRNA-based therapeutics appears to hold great promise to combat cancer, at least for those cancers where other treatment options have plateaued. Further developments in miRNA-based therapeutics are anticipated to translate miRNA-based therapeutic strategies into a clinical reality and may create a paradigm shift in medicine and pharmaceutical industry.

Keywords: Anti-miR oligonucleotides, cancer, cancer therapy, cancerous cells, clinical trials, drug resistance, drug target, *in vivo* studies, miRNA inhibitor, miRNA masking, miRNA mimic, miRNAs sponges, miRNA therapeutics, mouse models, mRNAs, Non-coding RNAs, oncogenic miRNAs, pre-clinical trials, siRNAs, tumor suppressor miRNAs.

1. INTRODUCTION

The genesis of the current non-coding RNAs' (ncRNAs) scientific paradigm can easily be traced to the influential discovery of a microRNA (miRNA) gene in 1993 by a group led by Ambros [1]. Extensive research on these evolutionarily conserved, small, regulatory RNAs in the last decade has shown fascinating breakthroughs of recent times [2]. Concomitantly, experimental confirmation of the results attained by the human genome project further revealed that several transcripts are actually non-coding transcripts, and that miRNAs signify the most important class of ncRNA molecules. The involvement of miRNAs in the development of cancer was initially reported in 2002: since then, the role of miRNAs has been intensively investigated in manifold human disorders [3, 4]. The noteworthy increment in the number of patent application filings over the last 10 years reflects a considerable amount of novelty in this area.

miRNAs are currently considered as master regulators of the human genome [5]. Clinical and functional implications of miRNAs in various disorders have hauled up these tiny cellular components to the ranks of ideal drug targets [6]. In eukaryotes, they serve as significant modulators of gene expression. They influence the transcriptome and proteome by targeting protein coding transcripts, hence aiding in cell fate determination. Furthermore, miRNAs have loomed as vital molecules in cancer research and they have proved to hold potential in cancer. They have the ability to repress stability of protein-coding transcripts and cellular translation by targeting the 3′ untranslated regions (UTRs) in a sequential manner [7, 8]. This nature of selective silencing of gene expression by miRNAs is known to have a significant effect on human health and disease [9]. The therapeutic functioning of miRNA is based upon the catalytic process of the naturally occurring 15-22 nucleotide single stranded RNA, that enters the cytoplasmic multiprotein complex RNA-Induced Silencing Complex (RISC) to pair with mRNAs carrying complementary sequences and, as a result, repress

gene expression. Over 500 miRNAs of distinct nature have been identified in humans and more than 1000 have been predicted in total [10, 11]. Furthermore, exploration of the human genome sequences facilitated the discovery of the fact that miRNA genes frequently resides in fragile sites and genomic regions which are hot spots for chromosomal abnormalities [12]. Chromosomal abnormalities have been shown to be important for the etiology of various cancers. Various studies based on genome-wide approaches have reported strong association between various cytogenetic and molecular abnormalities and the location of miRNA genes [13 - 15]. Wey *et al*. investigated the genome-wide miRNA expression profiling in Intraductal papillary mucinous neoplasms (IPMNs) tissue and discovered six miRNAs (miR-100, miR-99b, miR-99a, miR-342-3p, miR-126, miR-130a) that may differentiate 'high-risk' IPMNs from 'low-risk' IPMNs [14]. Faltejskova *et al*. studied genome-wide miRNA expression profiling in colorectal cancer patients in order to discover miRNA signatures (miR-122, miR-122*, miR-885-5p, miR-10b, miR-143, and miR 28-5p) that would enable differentiation between primary tumors and their corresponding matched liver metastases [15, 16].

The ability of miRNAs to target multiple genes may hold the key to therapeutic accomplishment in cancer which is a heterogenic disease and cannot be effectively treated by targeting a single gene of interest. Calin *et al*. first reported the role of miRNAs in cancer through the characterization of chromosome 13q14 done on chronic lymphocytic leukemia [3]. Successively, numerous studies gave strong evidences of deregulated miRNA expression in the hallmarks of cancer [17, 18]. In cancer, various cellular mechanisms are involved in the miRNA dysregulation such as genetic mutations [19], aberrant DNA methylation [20] and histone acetylation [21] along with alternative splicing, changes in the miRNA processing machinery and polyadenylation may cause hindrance in the maturation of miRNA [9, 22]. Abnormal gain or loss of miRNAs plays a role in initiation, progression, and metastasis and drug resistance in a variety of cancers. They can act as either oncogenes or tumor suppressors, depending upon the pathway or genes they impact. For instance, miRNAs of the let-7 family are a class of tumor suppressors. Let-7 expression has been reported to be downregulated in breast, head, neck, ovarian, lung and prostate cancers [23]. Additional miRNAs, namely miR-17/92 cluster, miR-221, miR-222, miR-21, miR-155 and miR-9 are upregulated in various cancers [24]. The therapeutic and diagnostic significance of miRNAs is remarkable since they have unique profiles and high stability in biological samples. For cancer therapy, miRNA expression modulation is under investigation but therapeutic tempering is attained by oncogenic inhibition of miRNAs, or by altering tumor suppressor miRNAs [9]. Furthermore, Phytonutrients that modulate expression and action of miRNA which are functionally involved in cancer pathobiology may have a potential to consider as a

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