3.2.1 Number of papers published per teacher in the Journals notified on Peer Reviewed Journals website during the year .

Sr. No	Title of paper	Name of the author/s	Department of the teacher	Name of journal	Year of publication	ISSN number
1	The Impact of COVID-19 on Different Sectors of the Indian Economy	Prof.(Dr.)B.B. Landge	Commerce	National Journal of Research In Marketing, Finance & HRM	Oct.2021	ISSN – 2455-5398
2	Opportunities and Challenges of E-Recruitment	Prof.(Dr.)B.B. Landge	Commerce	National Research Journal of Management and Commerce	Apr-22	ISSN 2348-9766
3	The Role of IPR in Protection of various elements: An overview	Prof.(Dr.)B.B. Landge	Commerce	National Journal of Research In Marketing, Finance & HRM	Mar-22	ISSN – 2455-5398
4	'Make in India Scheme, Sustainability and Small-Scale Manufacturing Companies'	Prof. Tayade A.P.	Commerce	Mechanical Engineering Vol.6 special issue 'Kalahari' Journal	Dec.2021	ISSN 0974-5823.
5	An Overview on New Era in Business- E-Commerce'	Prof. Tayade A.P.	Commerce	VIDYAWARTA	FEB.2022	ISSN 2319-9318.
6	'The Role of IPR in Protection of Various Elements: Overview Vol.7-Issue I	Prof. Tayade A.P.	Commerce	National Journal of Research In Marketing, Finance & HRM	Mar-22	ISSN 2455-5398
7	Corporate Social Responsibility	Prof. Dr. Wakhare P.B.	Commerce	National Journal of Research In Marketing,	Mar-22	ISSN 2455-5398
8						

9	**The Creation of particular learning methods for Blind Children**	**Prof. Dr. Wakhare P.B.**	**Commerce**	**VIDYAWARTA**	**01-Mar-22**	**ISSN 2319-9318.**
10	**Corporate Social Responsibility Dislosures In selected Indian Companies**	**Prof. Borhade B.S.**	**Commerce**	**National Journal of Research In Marketing, Finance & HRM**	**Mar-22**	**ISSN 2455-5398**
11	**The study on the relationship between employee motivation and work performance**	**Prof. Sonam R.Patwa**	**Commerce**	**International journal of advance and innovative research**	**31-Oct-21**	**ISSN 2394-7780**
12	**Employee motivation and employee welfare**	**Prof. Sonam R.Patwa**	**Commerce**	**Bangal, past & present journal of Culcatta Historical society**	**July-sept, 2021**	**ISSN01-05-8807**
13	**Impact of financial & non-financial incentives on employee motivation & performance**	**Prof. Sonam R.Patwa**	**Commerce**	**International Research Journal of Human Resource and Social Sciences**	**Mar-22**	**ISSN(O): (2349-4085) ISSN(P): (2394-4218)**
14	**A study of employee motivation and job satisfaction for organizational performance**	**Prof. Sonam R.Patwa**	**Commerce**	**Vidyawarta Peer reviewed international journal**	**Mar-22**	**ISSN: 2319 9318**
15	**HRM – Training & Development programme**	**Prof. Sonawane R.K.**	**Commerce**	**National Journal of Research In Marketing, Finance & HRM**	**Oct. 2021**	**ISSN -2455-5398**
16	**Advantages & Disadvantages of online education**	**Prof. Sonawane R.K.**	**Commerce**	**Vidyawarta Peer reviewed international journal**	**Mar. 2022**	**ISSN – 2319-9318**

17	The impact of branding on consumer buying behaviour	Prof.Gaikwad J.R.	Commerce	National Journal of Research In Marketing, Finance & HRM	Oct. 2021	ISSN – 2455-5398
18	A study on recruitment & selection process of organisation with the help of recruitment agencies	Prof.Gaikwad J.R.	Commerce	Vidyawarta Peer reviewed international journal	Mar-22	ISSN – 2319-9318
19	श्रीराम परिहार के पानी हैं अनमोल निबंध में चित्रित व्यंग्यात्मकता	Dr.S.V.Gaikwad	Hindi	Shodh – Rityu peer Reviewed Refereed Journal April – Jun 2021	2021	ISSN: 2454-6283
20	टेलीफिल्म की संवाद योजना : एक अध्ययन	Dr.S.V.Gaikwad	Hindi	peer Reviewed International Multilingual Research Journal July 2021	Jul-21	ISSN : 2394 -5303
21	प्रयोजनमूलक हिन्दी का महत्व	Dr.S.V.Gaikwad	Hindi	UGC Care listed group I Journal	Jul-21	ISSN: 0975 – 7945
22	आपका बंटी उपन्यास में चित्रित बाल मनोविज्ञान	Dr.S.V.Gaikwad	Hindi	Peer Reviewed Research Journal	Jun-21	ISSN: 2320-4494
23	बैरिस्टर' का हिंदी अनुवाद : द्वंद्वात्मकता और संतुलन	Dr.S.V.Gaikwad	Hindi	Research Hub International Multilingual Research Journal Feb-2022	Feb-22	e-ISSN:2349-7637

24	रजिया: एक आदर्श रेखाचित्र Page	Dr.S.V.Gaikwad	Hindi	International peer Reviewed Refereed Journal Surabhi Feb-2022	Feb-22	ISSN-2349:4557
25	मराठी नाटक 'तुझे आहे तुजपाशी' की अनुवादानुकूलता	Dr.S.V.Gaikwad	Hindi	Printing Area April-2022	Apr-22	ISSN-2394-5303
26	उपन्यासकर संजीव कृत लिखित फाँस उपन्यास में चित्रित किसान जीवन	S.N.Kokate	Hindi	A Multidisciplinary International Level Refered Journal peer Reviewed Journal Oct 2021	Oct-21	ISSN 2230 9578
27	1. Floristic studies on studies on Nawegaon Nagzira Tiger	Dr. D. N.Patil	Botany	International Journal of Research and development		2230- 9578Volume - 10
28	Wild relative	Dr. D. N.Patil	Botany	International journal of Scientific research in Science and Technology		2395-6011 Volume - 9

29	**SAMPLING DISTRIBUTION OF SAMPLE MEAN AND SAMPLE MAXIMUM UNDER SIMPLE RANDOM SAMPLING AND STRATIFIED SAMPLING: A COMPARATIVE STUDY**	**Mr. C. G. Shelake**	**Statistics**	**Vidyabharati International Interdisciplinary Research Journal (Special Issue)**	**octomber 2021**	**ISSN 2319-497**
30	**Dr. Babasaheb Ambedkaranche arthik vichar:chalan, sheti, kamgar,udyogdhande**	**Mr. Subhash Bajirao Shinde**	**Economics**	**Contribution of Mahatma Phule and Dr. Babasaheb Ambedkar in making of Modern India**	**2021-22**	**2304-5890**
31	**Synthesis, Characterization of Rhodamin 6G Capped Gold Nanoparticles and Sensing Reactive Oxygen Species**	**Mr.Gopale R.D.**	**Chemistry**	**Wesleyan Journal of Research,**	**Vol.14 No.25 (September 2021)**	**ISSN – 0975-1386**

32	Biocatalytic transformations of bioactive labdanediterpenoids from Andrographispaniculata (Burm f.) Nees: A review, Biocatalysis and Biotransformation,.	Dr.Swati Kolet	Chemistry	Biocatalysis and Biotransformation	Nov 2021 Volume 40, Issue 5	10292446
33	Design, synthesis of anticancer and anti-inflammatory 4-(1-methyl-1H-indol-3-yl)-6-(methylthio) pyrimidine-5-carbonitriles	Dr.Swati Kolet	Chemistry	SYNTHETIC COMMUNICATION	March 2022 Volume 52, Issue 5	397911
34	Microwave assisted synthesis and study of thermal effect of Quinone and Arylamide polymer	D.D.Gaikwad	Chemistry	Research journal in Chemistry	Sep-22	
35	Thermo Study of Commercial Samples of Lohabhasma	Dr.R.A.GULLKARI	Chemistry	Maharaja Sayagirao Journal Badoda	Nov-21	ISSN : 0025-042 Only Print Version
36	Sodium Alginate Biopolymer: An Effcient Recyclable green Catalyst for the Synthesis of Chalcone Derivatives under Mil Conditions	Dr. M.A.Bora	Chemistry	Macromolecular Symposia	Aug-22	ISSN 1521-3900

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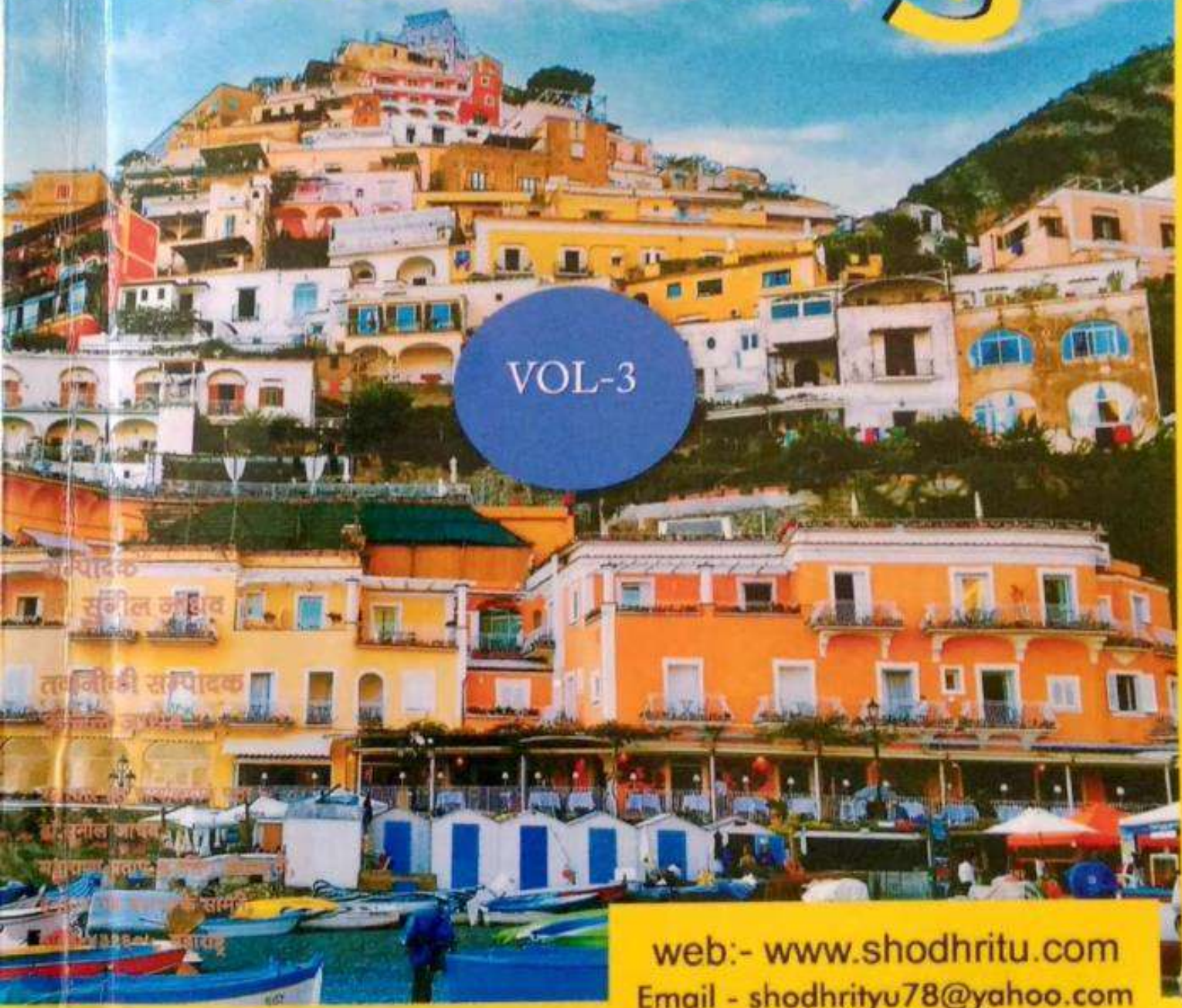

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क-अधिगम एवं
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3.मिश्र, विनीत
ारती प्रकाशन

37.श्रीराम परिहार के 'पानी है अनमोल' निबंध में चित्रित व्यंग्यात्मकता

-डॉ.सिध्देश्वर दि.गायकवाड
सहयोगी प्राध्यापक व हिंदी विभाग प्रमुख, भारतीय जैन संघटना का कला,विज्ञान व वाणिज्यमहाविद्यालय, वाघोली ता.हवेली,पुणे.

निबंध आधुनिक हिंदी गदय की महत्वपूर्ण विधा है। प्राचीन षरतीय साहित्य में निबंध का वर्तमान स्वरुप प्राप्त नही है। षरतीय साहित्य में निबंध शब्द अनेक अर्थों मे प्रयुक्त हुआ है। किसी विषय पर अपने विचार प्रकट करने का प्रयास ही निबंध है। निबंध का शाब्दिक अर्थ है-सूत्रों में आबद्ध, गठी हुई रचना। निबंध शब्द मूलतः संस्कृत का है, जिसका अर्थ है बाँधना या श्रृखला बध्द करना। निबंध के जन्मदाता फ्रांसीसी लेखक माइकेल द. मोन्तेन हैं। प्रसिध्द आलोचक डॉ. श्यामसुदर दास ने लिखा है-"निबंध उस लेख को कहना चाहिए जिसमें किसी गहन विषय पर विस्तारपूर्वक और पाण्डित्यपूर्ण विचार किया गया हो।"[1] आ. रामचंद्र शुक्ल निबंध की व्याख्या करते हुए लिखते हैं-"यदि गदय कवियों या लेखकों की कसोटी है तो निबंध गदय की कसौटी है। षषा की पूर्ण शक्ति का विकास निबंधों में ही सबसे अधिक संभव होता है।"[2] निबंध की प्रमुख विशेषताओं में है कसावट, स्वत:पूर्णता, सम्बध्दता, प्रवाह, भाषा तथा उद्देश आदि। विषय निरुपण एकसूत्रता, व्यक्तित्व का अन्तर्भाव तथा कलात्मकता का समावेश निबंध के प्रमुख तत्वों में होता है। निबंध के प्रमुख प्रकारों में वर्णनात्मक, विवरणात्मक, विचारात्मक, भावात्मक, ललित, वैयक्तिक, व्यक्ति प्रधान, व्यक्तिनिष्ठ आदि आते हैं। निबंध विधा ने आज आशातीत प्रगति की है।

श्रीराम परिहार जी इक्कीसवी शती के श्रेष्ठ निबंधकार हैं। उच्च शिक्षित डॉ. परिहारजीने अपने ललित निबंधों से समकालीन निबंधकारों के बीच एक अलग पहचान बनायी है। सरल और सरस भाषा में लिखित इनके निबंध पाठकों के बीच बहुत लोकप्रिय हैं। अपने निबंधों में उन्होंने समाज और वर्तमान स्थितियों पर पैने व्यंग्य भी किए हैं। भाषा में सजीवता लाने के लिए इन्होंने स्थानीय शब्दों का भी प्रयोग किया है। श्रीराम परिहार जी साधारण विषयों को भी अपने अनुभव एवं गहन अध्ययन से सार्थक एवं चिंतनीय बनाते हैं। निबंध के अतिरिक्त उन्होंने गीत और समीक्षात्मक पुस्तकों का भी सृजन किया है, एक निबंधकार के रुप में परिहार जी का हिंदी साहित्य जगत में महत्वपूर्ण स्थान है। उनके चर्चित निबंध संग्रहों में हैं- आँच अलाव की, अंधेरे में उम्मीद, धूप का अवसाद, बजे तो बंशी गूँजे तो शंख, ठिठके पल

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टेलीफिल्म की संवाद योजना एक अध्ययन

डॉ.सिद्देश्वर विट्ठल गायकवाड
सहयोगी प्राध्यापक व हिंदी विभाग प्रमुख,
भारतीय जैन संघटना काकला, विज्ञान व वाणिज्य महविद्यालय, वाघोली, ता. हवेली जि.पुणे

आज के आधुनिक एवं वैज्ञानिक विकास के दौर में मोबाइल, इंटरनेट, संगणक जैसी सुविधाओं एवं इलेक्ट्रॉनिक मीडिया ने मनुष्य को यंत्रवत बनाकर समूचे विश्व को एक बनाया है । तकनीकी एवं ज्ञान, विज्ञान के इस विकसित युग में मानव जीवन की गहन अनुभूतियों और संवेदनाओं को प्रकट करने वाला एक आधुनिक माध्यम के रूप में टेलीविजन को देखा जा सकता है, जिसमें लेखन, दृश्य कल्पना, मंच निर्देशन, रूप–सज्जा के साथ संवाद लेखन अधिक महत्त्वपूर्ण कार्य है ।

पटकथा विषय वस्तु एवं चरित्र पर आधारित होती है और इनतत्वों को संचालित संवाद करते हैं । संवाद ही टेलीफिल्म को गतिशील बनाते हैं। नायक–नायिकाओं तथा अन्य पात्रों के चरित्र को उजागर बनाते है । संवाद ही व्यक्ति को अनुभूति की गहराइयों से परिचित कराते है । डॉ. लक्ष्मीकांत पांडेय के अनुसार– पूरी पटकथा संवाद में होती है, कथा की तरह पढ़ने के लिए पटकथा नहीं लिखी जाती है, वरन् इसे बोलने और सुनने के लिए लिखा जाता है । पात्रों की बातचीत में ही सारा कारोबार चलता है, इसीलिए सशक्त एवं सार्थक संवाद के अभाव में प्रवाहमयता नहीं आएगी, ना गति, न द्वंद्व भरेगा, न मजा आएगा इसीलिए हर दृष्टि से संवादों की सफलता और असफलता ही पूरे कार्यक्रम की सफलता असफलता का सबक बन सकती है।१

कथा, पटकथा, संवाद के माध्यम से ही टेलीफिल्म की कहानी आगे बढ़ती है, पटकथा का प्रारूप तैयार होता है । पटकथाकार को सहज, स्वाभाविक भाषा का ही प्रयोग करना चाहिए । बिंबो, प्रतिको तथा लक्षणा व्यंजनाओं की जगह अभी तक भाषा में बोले गए संवाद दर्शक के मन को प्रभावित करते है। आँचलिक, प्रचलित, कठिन संवाद दर्शक भी समझ नहीं पाते हैं । कहानी से पटकथा बनने की प्रक्रिया में घटनाओं को छोटे–छोटे दृश्य में विभाजित किया जाता है ।

डॉ. चंद्रप्रकाश मिश्र लिखते है –एक सर्वोत्तम पटकथा वही होती है,जिसमें दृश्य, संवाद,दूरी और कोण का स्पष्ट विश्लेषन होता हैं ।२

अत: पटकथा लेखन में विशेष सतर्कता की आवश्यकता होती हैं। पटकथा में विषय के प्रतिपादन में जिन प्रसंगो अथवा घटनाओं आदि का सहयोग लिया जाता है, उनका संयोजन इस प्रकार से किया जाना चाहिए कि दर्शक के सम्मुख क्रम से आने वाले प्रत्येक दृश्य में उसकी उत्सुकता और जिज्ञासा धीरे–धीरे विकसित होती चली जाए, परंतु इसके लिए पटकथाकार के पास लेखन की कल्पनात्मक शक्ति होनी चाहिए। संवाद और पटकथा लेखन दोनों एक दूसरे के बिना अधूरे है, लेकिन इसके बावजूद फिल्मों में पटककथा अलग लिखी गई है और संवाद अलग लिखे गए हैं।

साहित्य में संवाद नवीन जीवन दृष्टि के साथ कल्पना जगत का निर्माण करते हैं, जबकि टेलीफिल्म के संवाद कथा को गति देने के साथ मनोभावों को कलात्मक रूप से व्यक्त करते है ।– 'ईदगाह' टेलीफिल्म के संवाद देखिए–

–हामिद (जावेद खान) : दादी, सभी तो नए कपड़े पहनके आएँगे, ईदगाह में और मैंवहीफटा पुराना पाजामा। महमूद शेरवानी पहन के जा रहा है।

अमीना (सुरेखा सिकरी): तू ईदगाह थोड़े ही जा रहा है।

हमीद (जावेद खान) : क्यों नहीं जा रहा हूँ, ईदगाह? सभी तो जा रहे हैं।

अमीना : देखो बेटा, उन्हें तो बड़ी–बड़ी ईदी देंगे माँ दूबाप, मेरे पास पैसे कहा पैसे कहा, जो तुझे ईदी दूँगी।३

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प्रयोजनमूलक हिंदी का महत्व

डॉ. सिद्धेश्वर विठ्ठल गायकवाड
सहयोगी प्राध्यापक व हिंदी विभाग प्रमुख, भारतीय जैन संघटना का कला विज्ञान व वाणिज्य महाविद्यालय, वाघोली ता.हवेली जि.पुणे.

प्रस्तावना:
प्रयोजनमूलक हिंदी अंग्रेजी शब्द फंक्शनल हिंदी का पर्याय है। प्रयोजनमूलत हिंदी के लिए कई समानार्थक शब्द मिलते हैं जैसे -फंक्शनल हिंदी, कामकाजी हिंदी, हिंदी कार्मिकी, व्यवहारिक हिंदी, व्यवसायिक हिंदी, आदि इनमें से हमें सबसे उपयुक्त पर्याय प्रयोजनमूलक हिंदी ही लगता है। प्रयोजन मूलक हिंदी को अधिक स्पष्ट करते हुए डॉ. सु. नागलक्ष्मी लिखती हैं - "प्रयोजनमूलक शब्द प्रयोजन शब्द में मूलक प्रत्यय लगने से बना है। प्रयोजन से तात्पर्य है उद्देश्य। मूलक से तात्पर्य है आधारित।अतएव, प्रयोजनमूलक भाषा का अर्थ है - किसी विशिष्ट उद्देश पर आधारित भाषा। दूसरे शब्दों में कहें, तो यह एक ऐसी विशिष्ट भाषा है, जिसका प्रयोग किसी विशिष्ट प्रयोजन या उद्देश के लिए किया जाता है। सामान्य लकीर से हटकर शिक्षा को वास्तविक पहलू से जोडना ही प्रयोजनमूलक हिंदी का उद्देश है।"[1]
आज प्रत्येक व्यक्ति अपनी जीविका चलाने के लिए रोजगारपरख शिक्षा लेना चाहता है।प्रयोजनमूलक हिंदी में रोजगार उपलब्ध कराने की क्षमता है,जिससे उसका महत्व बढता जा रहा है।प्रयोजनमूलक हिंदी के संदर्भ में छात्र की दृष्टि से विचार करने पर स्पष्ट हो जाता है कि आज ज्ञान-विज्ञान, पारिभाषिक शब्दावली, विज्ञापन, अनुवाद,सरकारी पत्राचार, आवेदन पत्र, संक्षेपण, प्रारूप लेखन,परिपत्र,समाचार लेखन ,अन्य माध्यमों के लिए वार्ता लेखन इ. क्षेत्रों में रोजगार के अवसर उपलब्ध हो रहे हैं।
इन अवसरों को प्राप्त करने के लिए छात्र में प्रयोजनमूलक हिंदी को पढने की आवश्यकता को बराबर महसूस किया जा रहा है। छात्रों को उपर्युक्त बिंदुओं में से कुछ मूलभूत बिंदुओं की ओर ध्यान आकर्षित करने के उद्देश्य से प्रस्तुत आलेख निर्माण करने की योजना है। इस में प्रयोजनमूलक हिंदी में बार - बार प्रयुक्त होनेवाली अवधारणाओं को छात्रों को उपलब्ध कराया गया है।प्रयोजनमूलक हिंदी में से केवल निम्नलिखित मुद्दों का इस आलेख में अंतर्भाव किया गया है।
[1.]संवाद लेखन
[2.]संक्षेपण लेखन
[3.]पारिभाषिक शब्दावली
[4.]समाचार लेखन

संवाद लेखन:
दो या दो से अधिक व्यक्तियों के बीच हुए वार्तालाप को संवाद कहते है। संवाद में कम से कम दो लोगों का भाग लेना अनिवार्य है। संवाद के माध्यम से वक्ता श्रोता के बीच प्रतिक्रिया अनुक्रिया का सिलसिला प्रारंभ होता है। वक्ता के मन की बात श्रोता के कानों तक पहुँच जाती है। विचारों और भावों की अभिव्यक्ति संवादों के अभाव में संभव नहीं है। संवाद जितने सजीव, सामाजिक एवं रोचक होंगे उतने ही वे आकर्षक होंगे। अच्छे संवाद लेखन की कुछ विशेषताएँ बताते हुए डॉ. वासुदेव नंदन प्रसाद लिखते हैं-
"1. संवाद में प्रवाह,क्रम और तर्कसंमत विचार होना चाहिए।
2. संवाद देश, काल व्यक्ति और विषय के अनुसार लिखा होना चाहिए।
3. संवाद सरल भाषा में लिखा होना चाहिए।
4. संवाद में जीवन की जितनी अधिक स्वाभाविकता होगी, वह उतना ही अधिक सजीव, रोचक और मनोरंजन होगा।
5.संवाद छोटे और स्पष्ट होने चाहिए। तभी उसके प्रति पाठकों का आकर्षण बढेगा।
6. संवाद का आरंभ और रोचक हो।"[2]

संक्षेपण:
प्रयोजनमूलक हिंदी का एक महत्वपूर्ण बिंदु संक्षेपण है। संक्षेपण में लंबे चौढे विवरण को संक्षिप्त एवं क्रमबद्ध रूप में प्रस्तुत किया जाता है जिससे मूल विस्तृत संदर्भ पढने की आवश्यकता नहीं होती। इस संदर्भ में डॉ. वासुदेव नंदन प्रसाद लिखते हैं - " किसी विस्तृत विवरण, विस्तार व्याख्या, वक्तव्य, पत्रव्यवहार या लेख के तथ्यों और निर्देशों के ऐसे संयोजन को संक्षेपण कहते है, जिसमें अप्रासंगिक, असंबद्ध, पुनरावृत्त, अनावश्यक बातों का त्याग और सभी अनिवार्य, उपयोगी तथा मूल तथ्यों का प्रवाहपूर्ण संक्षिप्त संकलन हो।"[3]
उक्त परिभाषा में संक्षेपण के समस्त तत्व विद्यमान हैं।संक्षेपण के गुणों में उल्लेखनीय हैं -1.पूर्णता 2.संक्षिप्तता 3.स्पष्टता 4.भाषा की सरलता 4.शुद्धता 5.प्रवाह और क्रमबद्धता आदि।
संक्षेपण के तत्व और उसके गुणों को ध्यान में रखते हुए किया गया संक्षेपण अपने आप में अद्वितीय होता है,जो प्रयोजनमूलक हिंदी का एक अंग है।

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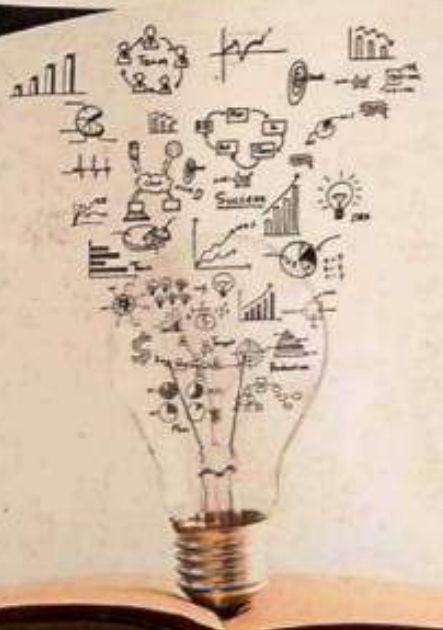

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आपका बंटी उपन्यास में चित्रित बाल मनोविज्ञान

डॉ. सिध्देश्वर विठ्ठल गायकवाड
सहयोगी प्राध्यापक व हिंदी विभाग प्रमुख
भारतीय जैन संघटना का कला विज्ञान व वाणिज्य महाविद्यालय वाघोली ता. हवेली जि. पुणे

प्रस्तावना :

हिंदी गद्य विधाओं में उपन्यास अत्यंत सशक्त विधा है। अन्य विधाओं की तुलना में उपन्यास का कैनवास व्यापक होता है। मानव जीवन के समग्र घटना प्रसंगों को बडी सूक्ष्मता के साथ उपन्यास में चित्रित किया जाता है।उपन्यास का सही विकास प्रेमचंद युग में हुआ है। स्वातंत्र्योत्तर उपन्यासों में आधुनिकता को लेकर विस्तार से चर्चा हुई है। विशेषतः ग्रामीण,मनोवैज्ञानिक,प्रगतिवादी, महानगरीय, आँचलिक के साथ-साथ स्त्री विमर्श, दलित विमर्श, मुस्लिम विमर्श, आदिवासी विमर्श, तथा किन्नर विमर्श आदि विषयों को बारिकी से उकेरा गया है। सन 1960 के बाद महिला लेखिकाओं ने बडी संख्या में लेखन कार्य प्रारंभ किया। इन्होंने मानव जीवन की आपा धापी,अर्थ केंद्रित जीवन शैली, नष्ट होते एवं बदलते मूल्य,यांत्रिक सभ्यता को उपन्यासों में बडी सादगी के साथ चित्रित किया है। आधुनिक महिला लेखिकाओं में महेंद्र कुमारी उर्फ मन्नू भंडारी का अत्यंत महत्त्वपूर्ण स्थान है। 'मै हार गई' कहानी मन्नू भंडारी की प्रसिद्धी का कारण बनी। यहाँ से कथा साहित्य में मन्नू जी ने एक नवीन प्रयोग कर अपनी स्वतंत्र पहचान बनाई। सन 1971 में प्रकाशित "आपका बंटी" मन्नू भंडारी काही नहीं समग्र हिंदी साहित्य का अनमोल रत्न है। "आपका बंटी मन्नू भंडारी के उन बेजोड उपन्यासों में से हैं जिनके बिना न बीसवी शताब्दी के हिंदी उपन्यास की बात की जा सकती है न स्त्री विमर्श को सही धरातल पर समझा जा सकता है।"[1] उक्त उपन्यास हिंदी की लोकप्रिय पुस्तको की पहिली पंक्ति में आता है।

1.आपका बंटी में चित्रित बालमनोविज्ञान:

आपका बंटी लेखिका मन्नू भंडारी का स्वतंत्र रूप से लिखा गया प्रथम उपन्यास है। उपन्यास की स्थूल कथा अत्यंत संक्षिप्त है। शकुन, अजय और बंटी तीन प्रमुख पात्रों के माध्यम से लेखिका ने आधुनिक मानव जीवन की त्रासदी का बडा मार्मिक चित्रण किया है। आधुनिक सुशिक्षित पति-पत्नी के अहं के टकराव तथा तनावों से उत्पन्न स्थितियों के बीच संबं- विच्छेद की भूमिका की निर्मिती होते जाना,

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Abstract

Barrister is a famous Marathi play written by Jayvant Dalvi. Dalvi ji is recognized as a fine writer in the Marathi theater field. Barrister is a dramatization published in 1977. Three years after the original was published, Dr. Vijay Bapat translated it into Hindi in 1980 and placed it in front of the theater-loving readers of the Hindi region. The play deals with social themes, in which the pathetic condition of widows has been clarified. Dr. Vijay Bapat has translated it into Hindi as this topic is new for Hindi theatrical lovers. It is not possible to discuss the entire dramatization here because of the fear of expansion. That's why we are discussing here the English translation of the Barrister: dialectics and balance only. Translation always has to strike a balance between the two situations, like- original author translator, original author and other readers, cohesiveness and equanimity, original text translated text, Native Language Idioms and Translated Language Idioms.

Keywords: *original author translator, original author and other readers, cohesiveness and equanimity, original text translated text*

Abstract in Hindi

बैरिस्टर जयवंत दलवी द्वारा लिखा गया मराठी का प्रसिद्ध नाटक है। दळवी जी मराठी नाट्य क्षेत्र के अतिरिक्त ललित लेखक के रूप में मान्यता प्राप्त है।बैरिस्टर 1977 में प्रकाशित नाट्यकृति है। मूल रचना के प्रकाशित होने के तीन साल बाद डॉ.विजय बापट ने इसे 1980 में हिंदी में अनूदित कर हिंदी प्रदेश के नाट्यप्रेमी पाठकों के सामने रखा। नाटक सामाजिक विषय से संबंधित है, जिसमें विधवाओं की दयनीय अवस्था को स्पष्ट किया गया है। हिंदी नाट्य प्रेमियों के लिए यह विषय नया होने के कारण डॉ.विजय बापट ने इसे हिंदी में अनूदित किया है। संपूर्ण नाट्यानुवाद की यहाँ चर्चा करना विस्तारभय के कारण संभव नहीं है। इसलिए हम यहाँ बैरिस्टर का हिंदी अनुवाद : द्वंद्वात्मकता और संतुलन यही तक सीमित रहकर चर्चा कर रहे है। अनुवाद में हमेशा दो स्थितियों में संतुलन स्थापित करना पडता है। जैसे– मूल लेखक अनुवादक, मूल लेखक तथा दूसरे पाठक, सामासिकता और उद्रिक्तता, मूल पाठ अनूदित पाठ, मूल भाषा के मुँहावरे अनूदित भाषा के मुँहावरे

Keywords: *मूल लेखक अनुवादक, मूल लेखक तथा दूसरे पाठक, सामासिकता और उद्रिक्तता, मूल पाठ अनूदित पाठ*

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भूमिका:

'बैरिस्टर' जयवंत दलवी दवारा लिखा गया मराठी का प्रसिद्ध नाटक है। दलवी जी मराठी नाट्यक्षेत्र के अतिरिक्त ललित लेखक के रूप में मान्यता प्राप्त हैं। उन्होंने कहानी, उपन्यास, एकांकी तथा कई नाटक लिखे हैं। उनके नाटक निम्नानुसार हैं–

1. संध्याछाया 2. बॅरिस्टर 3. सूर्यास्त 4. महासागर 5. दुर्गी 6. सभ्यगृहस्थ हो 7. सावित्री 8. पुरुष 9. पर्याय 10. मुक्ता 11. हरी–अप–हरी! 12. स्पर्ष 13. कालचक्र 14. मी राष्ट्रपती 15. लग्न आदि।

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रजिया: एक आदर्श रेखाचित्र

प्रो.(डॉ.) सिद्धेश्वर विट्ठल गायकवाड
प्रोफेसर व अध्यक्ष हिंदी विभाग,
भारतीय जैन संघटना का कला
विज्ञान व वाणिज्य महाविद्यालय,
वाघोली ता.हवेली जि.पुणे

भूमिका:

रजिया रामवृक्ष बेनीपुरी लिखित एक आदर्श रेखाचित्र है। रेखाचित्र की चर्चा करने के पहिले संक्षेप में रामवृक्ष बेनीपुरी का परिचय लेना जरुरी होगा। " रामवृक्ष बेनीपुरी बहिर्मुखी व्यक्तित्ववाले कलाकार थे। वे जनता में जाते थे। कई लोगों से मिलते थे। इस प्रकार के संपर्क से वे अपने साहित्य के लिए अनुभव प्राप्त करते थे; विषय जुटाते थे। उनका साहित्य जो इतना जीवन के निकट है, उसका यही कारण है। विविध कला क्षेत्रों से अनुभव की पूँजी इकट्ठा करने में बेनीपुरी की रुचि थी। उनकी मान्यता थी कि कला संबंधी पुस्तकें पढ़कर कला का ज्ञान ग्रहण करना जितना जरूरी है उससे कई गुणा जरूरी है कला को प्रत्यक्ष देखना। कला से रू-ब-रू होने का आनन्द अनूठा होता है। कलाकारों से मिलकर तो उन्हें अपूर्व आनन्द होता था। अतः वे कलाकारों से मिलने का अवसर कभी खोते नहीं थे। फिर वे कलाकार चित्रपट-जगत् के हों, शिल्प तथा मूर्तिकला क्षेत्र के हों, लोक कला से संबंधित हों या साहित्य-संसार के विविध कलाकारों से मिलने के कितने ही सुखद प्रसंग बेनीपुरी ने अपनी डायरी में शब्दबद्ध किए हैं।

शिवपूजन सहाय, माखनलाल चतुर्वेदी, हरिवंशराय बच्चन, पदुमलाल पुन्नालाल बख्शी, उपेन्द्रनाथ अश्क, रामधारी सिंह दिनकर, सुमित्रानंदन पंत, महादेवी वर्मा, पांडेय बेचन शर्मा 'उग्र', राजा राधिकारमण सिंह, पृथ्वीराज कपूर, राजकपूर, अशोक कुमार, स्नेहप्रभा प्रधान आदि विख्यात कलाकारों से हुई मुलाकातों के प्रसंग प्रस्तुत डायरी में मिलते हैं।"[1]

रामवृक्ष बेनीपुरी का जन्म 23 दिसम्बर, 1899 को बेनीपुर गाँव, जिला-मुजफ्फरपुर (बिहार) में एक साधारण किसान परिवार में हुआ था। उनके पिता का नाम श्री फूलवन्त सिंह था बालक रामवृक्ष को बच्चा छोड़कर माता जी के स्वर्ग सिधारने के बाद इनका लालन-पालन बंशीपचडा गाँव में मामा के घर हुआ। उन्होंने यहीं पर प्रारम्भिक शिक्षा प्राप्त की। भूमिहार ब्राह्मण कॉलेजिएट स्कूल, मुजफ्फरपुर में कक्षा आठवीं में पढ़ते हुए हिन्दी साहित्य सम्मेलन, प्रयाग से 'विशारद' की परीक्षा पास की मैट्रिक में ही पढ़ाई छोड़कर 'असहयोग आन्दोलन में भाग लिया। सन् 1921 में पत्रकारिता के क्षेत्र में प्रवेश के साथ ही बेनीपुरी जी के साहित्यिक व्यक्तित्व का निर्माण शुरू हुआ। वे करीब-करीब एक दर्जन से अधिक पत्र-पत्रिकाओं के सम्पादक रहे। देश की पराधीनता और ब्रिटिश शासन की कठोरता के खिलाफ उनकी आत्मा में विद्रोह की भावना जाग्रत थी। उन्होंने 'युवक पत्र' का सम्पादन शुरू किया। सन् 1929 में युवक आश्रम की स्थापना की स्वतंत्रता आन्दोलन में 'युवक पत्र' को क्रान्तिकारी रूप से चलाया। परिणामतः उन्हें गिरफ्तार कर उनके 'युवक पत्र को बन्द किया गया, लेकिन बेनीपुरी जी की क्रान्तिकारी कलम रुकी नहीं। उन्होंने जेल से ही एक हस्तलिखित पत्र 'कैदी' का सम्पादन शुरू किया। स्वतंत्रता प्राप्ति के पश्चात् उन्होंने दो विदेश यात्राएँ की इंग्लैंड, स्कॉटलैंड, स्विट्जरलैंड, फ्रांस आदि देशों की पहली विदेश यात्रा सन् 1951 में हुई, जिसके अनुभवों पर 'पैरों में पंख बाँधकर' यात्रा पुस्तक लिखी गई तो सन् 1952 की दूसरी विदेश यात्रा पर 'उड़ते चलो-उड़ते चलो' यह यात्रा पुस्तक लिखी।

बेनीपुरी जी के स्वभाव में बचपन से ही मस्ती और चंचलता थी। सन् 1916 में उनकी पहली कविता 'प्रताप' में छपी। नाटक, एकांकी, उपन्यास, कहानी, निबन्ध, संस्मरण, शब्द चित्र रेखाचित्र, जीवनी और यात्रा साहित्य आदि विधाओं में आपने 60 से अधिक साहित्यिक रचनाओं का सृजन किया। उनका साहित्य केवल कल्पना विलासी नहीं है, उसमें तो जीवन की मिट्टी की सोंधी गन्ध है। उनके साहित्यिक व्यक्तित्व के लिए बनारसीदास चतुर्वेदी ने उन्हें सर्वश्रेष्ठ रेखाचित्रकार' की उपाधि दी तो मैथिलीशरण गुप्त ने उनकी कलम को 'जादू की छड़ी' कहा। माखनलाल चतुर्वेदी के शब्दों में उनकी लेखनी 'फौलाद उगलती है। शब्दों के सम्राट् बेनीपुरी जी के

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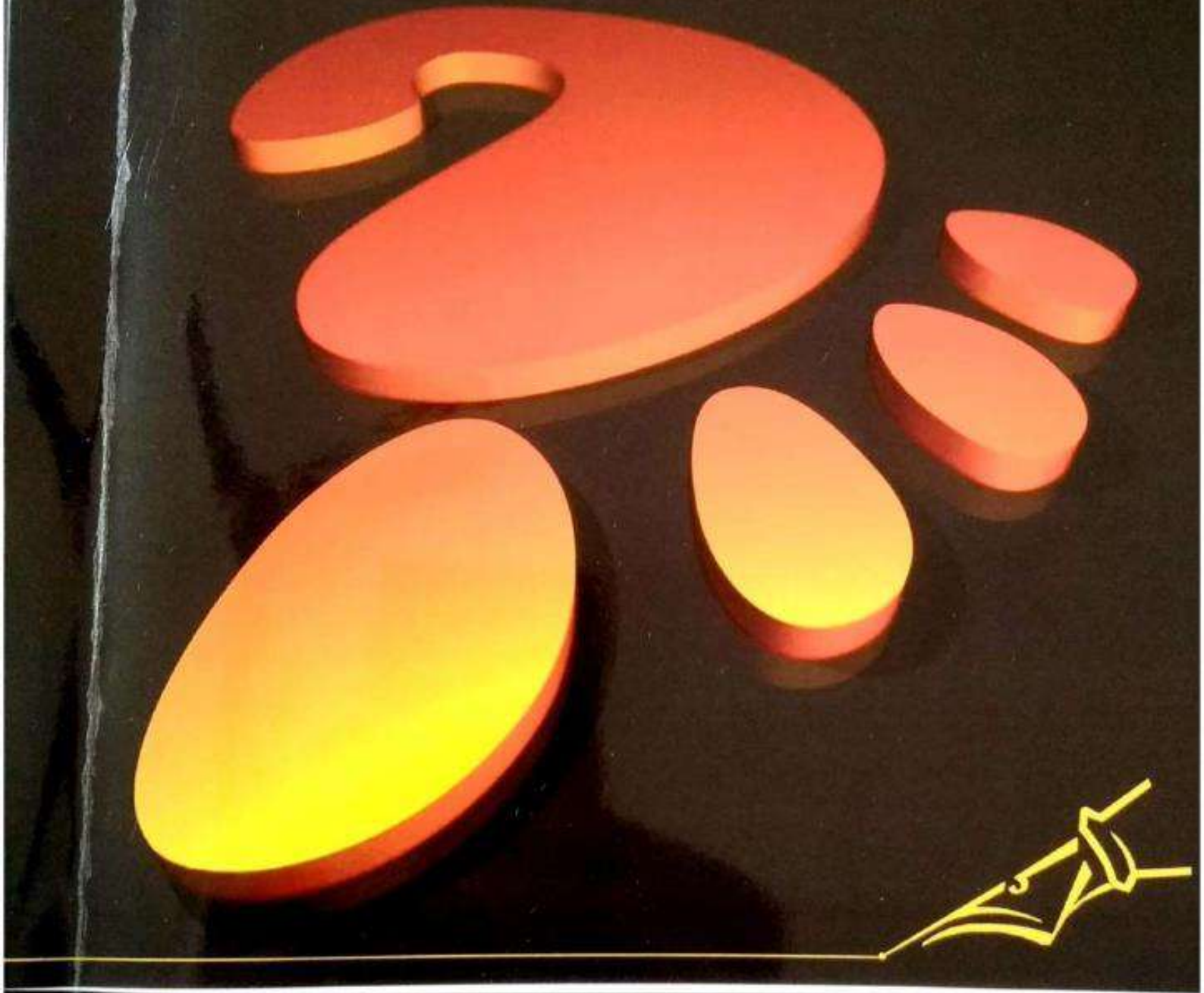

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बल्कि यह है कि उदारवादी विचारधारा के सामने अब कोई विचारधारा ही नहीं बची है उदारवादी विचारधारा ने अपने लक्ष्य को प्राप्त कर लिया है यह सर्वमान्य विचारधारा है ।

फ्रांसिस फुकोयामा की आलोचना भी हुई वास्तव में इतिहास के अन्त की बात उदारवादी और पूँजीवादी दायरे में ही सुनने को मिलती है। समाजवादी क्षेत्र में इसे कोई महत्व नही दिया गया। प्रश्न विचारधारा और इतिहास के अन्त का नहीं है वस्तुत: दोनों (उदारवादी और साम्यवादी) एक दूसरे के करीब आ रही है बात उनमें सहमति और सामजंस्य की है। मार्टिन सेलिगर ने कहा है "यदि इस व्याख्या को बारीकी से देखा जाये तो यह कहा जा सकता है कि जिस तथ्य की ओर इन दोनों लेखकों (बेल और लेन) ने हमारा ध्यान आकृष्ट किया है वह विचारधारा का अन्त नहीं बल्कि प्रमुख पक्षों के बीच वृहत्त विचारधारात्मक सहमति का उभरना है जिसने विचारधारा सम्बन्धी विवाद को पीछे धकेल दिया।"८

यद्यपि विचारधारा सम्बन्धी विवाद अपनी प्रासंगिकता खोता जा रहा है परन्तु विचारधारा की भूमिका को पूरी तरह से नकारा नही जा सकता है । राजनीति और विचारधारा को अलग नही किया जा सकता है यदि राजनीति सत्ता के लिए संघर्ष है तो उसको अनुप्रेरित करने वाली कोई न कोई विश्वास और प्रणाली भी होगी

सन्दर्भ सूची –

१. विचारधारा के अन्त से सम्बंधित विवाद पुस्तक राजनीति–सिद्धान्त की रूप रेखा पृष्ठ सं० ४३३ एवं ४३४ लेखक ओम प्रकाश गाबा, प्रकाशन–मयूर पेपर बैक्स ए–९५ सेक्टर–५ नोएडा

२. विचारधारा का अन्त– डॉ ए.के.वर्मा यू–ट्यूब

३. विचारधारा का अन्त, राजनीतिक संकल्पनाएं तथा विचारधाराए पृष्ठ सं० १७२ एवं १७३ लेखक जे. सी. जौहरी, प्रकाशन साहित्य भवन

४. उपर्युक्त

५. उपर्युक्त

६. Margdarshan for civil services (यू–ट्यूब)

७. उपर्युक्त

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मराठी नाटक 'तुझे आहे तुजपाशी' की अनुवादानुकूलता

डॉ. सिद्धेश्वर वि. गायकवाड
प्राध्यापक व हिंदी विभाग प्रमुख,
बी.जे.एस. कॉलेज, वाघोली, ता. हवेली, जि. पुणे

प्रस्तावना

'तुझे आहे तुजपाशी' मराठी के ख्यातनाम नाटककार, अभिनेता, कथाकथनकार पु. ल. देशपांडे की नाट्यकृति है। पु. ल. ने इसे १९५७ ई. में लिखकर मराठी नाट्यसाहित्य में एक नया मोड़ निर्माण किया। पु. ल. देशपांडे की नाट्यकृतियाँ निम्नानुसार हैं–

१. तुका म्हणे आता २. ती फुलराणी ३. अंमलदार ४. एक झुंज वाऱ्याशी ५. भाग्यवान ६. सुंदर मी होणार ७. तुझे आहे तुजपाशी ८. पहिला राजा (अनूदित) ९. तीन पैशाचा तमाशा आदि।

'तुझ आहे तुजपाशी' आरंभ में एक विनोद–पूर्ण वातावरण प्रधान नाटक लगता है। जैसे–जैसे नाटक समाप्ति की ओर चला जाता है वह जीवन की व्याख्या प्रस्तुत करते हुए गंभीर चिंतन की ओर चला जाता है। यहाँ हम मराठी 'तुझे आहे तुजपाशी' के हिंदी अनुवाद 'कस्तुरीमृग' कीअनुवादानुकूलतापर प्रकाश डालेंगे।

मराठी नाटक 'तुझे आहे तुजपाशी' की अनुवादानुकूलता

किसी रचना के अनुवाद का स्वरूप तथा उसकी सममूल्यता की मात्रा मूल सामग्री की अनुवादानुकूलता पर निर्भर करती है। अत: यह उचित होगा कि 'तुझे आहे तुजपाशी' के हिंदी अनुवाद के अध्ययन के आरंभ में ही मूल रचना की अनुवादानुकूलता पर प्रकाश डाला जाए।

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SAMPLING DISTRIBUTION OF SAMPLE MEAN AND SAMPLE MAXIMUM UNDER SIMPLE RANDOM SAMPLING AND STRATIFIED SAMPLING: A COMPARATIVE STUDY

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ABSTRACT

Traditional sampling designs provide an estimator of the population mean through the sample mean. The sample maximum receives very little attention. This paper gives the comparison of statistical properties of the sample mean and sample maximum under simple random sampling and stratified sampling. In particular, the sampling distribution of sample maximum is derived under simple random sampling and stratified sampling. The sampling distribution is then used to derive the expected value and sampling variance of sample maximum under these sampling designs.

***Keywords**: Sampling design, simple random sampling, sample mean, sample maximum, sampling distribution, sampling variance, stratified sampling.*

Introduction

One of the most common statistical procedures for collecting data that will be evaluated for inferential purposes is sampling. The population mean or population total has been emphasized as the most important population characteristic in the majority of the literature on finite population samples. As a result, the majority of statistical literature focuses on estimating the population mean or population total. In real life, the interest may not always be confined to the population mean or population. There are various scenarios in which the interest is in the population maximum.For example, the maximum temperature indicates the intensity of summer, and the severity of pollution is determined by the maximum level of pollutants present. In such instances, it obvious to use the sample maximum as an estimate of the population maximum. The sampling behavior of the sample mean and sample maximum is investigated in this work using various simple random sampling and stratified sampling. It is interesting to note that the sampling variability of the sample maximum as the sample size changes in comparison to the population size.

Estimation of Population Mean Under Simple Random Sampling

Simple random sampling (SRS) is a method used to draw a sample of n number of sampling unitsfrom a population which contains N sampling units, in such a way that every sampling unit of the population has an equal chance to include in the sample.There are two methods for drawing the samples.

Simple Random Sampling without Replacement (SRSWOR): In SRSWOR the units are randomly drawn one by one in such a way that, the unit selected will be again replaced, in the population before the next draw.

Simple Random Sampling with Replacement (SRSWR): In SRSWR the units are drawn one by one in such a way that the unit selected will not be replaced back in the population before the next draw.

Notations

Let the population contains the N sampling units $U_1, U_2, \ldots, U_N$ and sample contains the n sampling units $u_1, u_2, \ldots, u_n$.

Y is the characteristic under consideration

Yi (i = 1, 2,…,N) is value of the characteristic for the i^{th} unit of the population and yi (i = 1,2,…,n) is value of

the characteristic for the i^{th} unit of the sample. Then we define

$$\text{Population mean} = \overline{Y_N} = \frac{1}{N}\sum_{i=1}^{N} Y_i$$

$$\text{Sample mean} = \overline{y_n} = \frac{1}{n}\sum_{i=1}^{n} y_i$$

S^2 = Mean square for the population

$$= \frac{1}{N-1}\sum_{i=1}^{N}(Y_i - \overline{Y_N})^2$$

s^2 = Mean square for the sample

$$= \frac{1}{n-1}\sum_{i=1}^{n}(y_i - \overline{y_n})^2$$

σ^2 = population variance

$$= \frac{1}{N}\sum_{i=1}^{N}(Y_i - \overline{Y_N})^2$$

Probability of drawing a Sample and a Specified Unit

SRSWOR: If n sampling units are selected from population of size N by SRSWOR then the total possible samples are $\binom{N}{n}$. Therefore the probability of selecting any one of these samples is $\frac{1}{\binom{N}{n}}$.

The probability of drawing any unit at the 1st draw is 1/N, the probability of drawing any unit at 2nd draw from among the available (N-1) units, is 1/(N-1), and so on.

Let A_k be the event that any specified unit is selected at the k^{th} draw then

$$P(A_k) = \frac{1}{N}; k = 1, 2, \ldots, n$$

The probability of a specified unit including in the sample is

$$\sum_{k=1}^{n}\frac{1}{N} = \frac{n}{N}$$

SRSWR: If n sampling units are selected from population of size N by SRSWR then the total possible samples are N^n. Therefore the probability of selecting any one of these samples is $\frac{1}{N^n}$.

In SRSWR population size is remains the same at every draw, therefore the probability of selecting any element at any draw is 1/N.

In simple random sampling with replacement and without replacement, the sample mean is an unbiased estimator of the population mean.

i.e. $E(\overline{y_n}) = \overline{Y_N}$

The variance of the sample mean under SRSWOR is

$$Var(\overline{y_n}) = \left(\frac{1}{n} - \frac{1}{N}\right)S^2$$

$$= \frac{N-n}{nN}S^2$$

And the variance of the sample mean under SRSWR is

$$Var(\overline{y_n}) = \frac{N-1}{nN}S^2$$

Estimation of population mean Stratified Sampling

When the population is not homogeneous, simple random sampling is ineffective because some portions of the population may be overrepresented while others may be underrepresented. In these circumstances, the population is sub-divided into k strata in such a way that strata are internally homogeneous. This procedure of dividing the population into k strata is called as stratification. Stratification is done based on a characteristic that is closely related to the characteristics of the units being studied. After this process, a random sample is drawn from each stratum by using SRSWOR. All these units from different strata constitute a random sample from the population. Such a sample is called as a stratified random sample.

Between stratums, there is the maximal heterogeneity. This is why, when our aim is to estimate the population mean, sampling units are chosen from all strata, because each stratum contributes to the mean estimation.

Notations

Let k be the number of strata.

N: Total number of sampling units in the population, N_i : Number of sampling units ofi^{th} stratum, n_i : The number of sampling units selected by using SRSWOR from ith stratum, Y: characteristic under study, y_{ij} (j = 1,2,…,N_i, i = 1,2,...,k): value of j^{th} unit in the i^{th} stratum. $\overline{Y_{Ni}} = \frac{1}{N_i}\sum_{j=1}^{N_i} y_{ij}$: population mean of i^{th} stratum, $\overline{y_{ni}} = \frac{1}{n_i}\sum_{j=1}^{n_i} y_{ij}$: sample mean of i^{th} stratum, $w_i = \frac{N_i}{N}$, $n = \sum_{i=1}^{k} n_i$ and $N = \sum_{i=1}^{k} N_i$

In stratified samplingpopulation mean is weighted arithmetic mean of stratum means, weights being equal to size of strata and is given by $\overline{Y_N} = \frac{1}{N}\sum_{i=1}^{k} N_i \overline{Y_{Ni}}$. Sample mean is $\overline{y_n} = \frac{1}{n}\sum_{i=1}^{k} n_i \overline{y_{ni}}$ and $E(\overline{y_{ni}}) = \overline{Y_{Ni}}$

Now,

$$E(\overline{y_n}) = \frac{1}{n}\sum_{i=1}^{k} n_i E(\overline{y_{ni}})$$
$$= \frac{1}{n}\sum_{i=1}^{k} n_i \overline{Y_{Ni}}$$
$$\neq \overline{Y}_N$$

Here $\overline{y}_n$ is biased estimator of $\overline{Y}_N$. Now to obtain unbiased estimator of $\overline{Y}_N$ consider the stratum mean which is the weighted mean of strata sample means, weights being equal to size of strata given by $\overline{y_{st}} = \frac{1}{N}\sum_{i=1}^{k} N_i \overline{y_{ni}}$.

Now,

$$E(\overline{y_{st}}) = \frac{1}{N}\sum_{i=1}^{k} N_i E(\overline{y_{ni}})$$
$$= \frac{1}{N}\sum_{i=1}^{k} N_i \overline{Y_{Ni}}$$
$$= \overline{Y_N}$$

Thus $\overline{y_{st}}$ is an unbiased estimator of $\overline{Y}_N$.

$$Var(\overline{y_{st}}) = \sum_{i=1}^{k} w_i^2 \frac{N_i - n_i}{n_i N_i} S_i^2$$

Estimation of Population Maximum under Simple Random Sampling

Simple Random Sampling (SRS) provides an unbiased estimate of the population mean. This is the consequence of the fact that simple random sampling imposes a discrete uniform distribution on the finite population that is being sampled. The sample maximum is the most natural choice when the purpose is to estimate the population maximum. Statistical properties of the sample maximum are investigated here.

Let the population contains N sampling units $u_1, u_2, \ldots, u_N$. Let the variable of interest X, have values. $x_1, x_2, \ldots, x_N$ on these sampling units, respectively in that order. If the values $x_1, x_2, \ldots, x_N$ are organized in an ascending order of magnitude and written as $x_{(1)}, x_{(2)}, \ldots, x_{(N)}$, then the corresponding sampling units in the population also get reorganized and are recorded as $u_{(1)}, u_{(2)}, \ldots, u_{(N)}$. When a random sample of size n is selected by using SRSWOR from this population the sampling units in the sample are denoted by $U_{i_1}, U_{i_2}, \ldots, U_{i_n}$ and the corresponding values

of the variable of interest by $X_{i_1}, X_{i_2}, \ldots, X_{i_n}$. When sample values are sorted and organized in an ascending order of magnitude, the resulting values are written as $X_{(1)}, X_{(2)}, \ldots, X_{(n)}$ and the corresponding sampling units as $U_{(1)}, U_{(2)}, \ldots, U_{(n)}$. Since the n sample values are different (because SRSWOR), the sample maximum cannot take any of the n – 1 smallest values in the population, namely $x_{(1)}, x_{(2)}, \ldots, x_{(n-1)}$. It is then clear that the sample maximum $X_{(n)}$ can take any one of the N – n +1 possible values $x_{(n)}, x_{(n+1)}, \ldots, x_{(N)}$. If $X_{(n)} = x_{(r)}$, for some r such that $n \le r \le N$, then no sample value can exceed $x_{(r)}$. In other words, if $X_{(n)} = x_{(r)}$, then the other n – 1 sample values must be from among the r – 1 possible values $x_{(1)}, x_{(2)}, \ldots, x_{(r-1)}$. The number of ways in which such selection can be made is given by $\binom{r-1}{n-1}$ since the number of ways of selecting a sample of size n by using SRSWOR from a population of size N is $\binom{N}{n}$

The probability that the sample maximum is $x_{(r)}$ is given by

$$P\left[X_{(n)} = x_{(r)}\right] = \frac{\binom{r-1}{n-1}}{\binom{N}{n}} \text{ for } r = n, n+1, \ldots, N.$$

In other words, it is assumed that

$$x_{(r)} = r \quad \text{for } r = 1, 2, \ldots, N. \qquad (1)$$

This simplification leads to the simplified expression

$$P\left[X_{(n)} = r\right] = \frac{\binom{r-1}{n-1}}{\binom{N}{n}} \text{ for } r = n, n+1, \ldots, N.$$

Probability Distribution of the Sample Maximum

The largest sample value, that is the sample maximum, denoted by $X_{(n)}$, can take any one of the N – n+1 possible values n, n+1, n+2, …, N, When $X_{(n)} = r$ for some r = n, n+1, n+2, …, N, then one of the n sample values is exactly equal to r and the remaining n – 1 sample values are chosen from the r–1 possible values 1,2,…, r–1. The number of ways in which this can happen is $\binom{r-1}{n-1}$.

This leads to the expression

$$P\left[X_{(n)} = x_{(r)}\right] = \frac{\binom{r-1}{n-1}}{\binom{N}{n}}, r = n, n+1, \ldots, N. \qquad (2)$$

Since it is assumed that $x_{(r)} = r \quad \text{for } r = 1, 2, \ldots, N.$

It is also easy to write

$$P\left[X_{(n)} = r\right] = \frac{\binom{r-1}{n-1}}{\binom{N}{n}}, r = n, n+1, \ldots, N. \qquad (3)$$

Expected Value and Sampling Variance of the Sample Maximum

We use the probability distribution of the sample maximum given in Equation (3) to get the first two moments of the sample maximum. The expected value of sample maximum is given by

$$E\left[X_{(n)}\right] = \sum_{r=n}^{N} r.\, P\left[X_{(n)} = r\right]$$

$$= \sum_{r=n}^{N} r.\, \frac{\binom{r-1}{n-1}}{\binom{N}{n}}$$

$$= \frac{1}{\binom{N}{n}} \sum_{r=n}^{N} r.\, \binom{r-1}{n-1}$$

$$= \frac{1}{\binom{N}{n}} \sum_{r=n}^{N} r.\, \frac{(r-1)!}{(n-1)!(r-n)!}$$

$$= \frac{1}{\binom{N}{n}} \sum_{r=n}^{N} \frac{r!}{(n-1)!(r-n)!}$$

$$= \frac{n}{\binom{N}{n}} \sum_{r=n}^{N} \frac{r!}{n!(r-n)!}$$

$$= \frac{n}{\binom{N}{n}} \sum_{r=n}^{N} \binom{r}{n}$$

$$= \frac{n}{\binom{N}{n}} \binom{N+1}{n+1}$$

$$= n.\frac{n!(N-n)!}{N!} \cdot \frac{(N+1)!}{(n+1)!(N-n)!}$$

$$= \frac{N+1}{n+1}.n. \qquad (4)$$

The sample maximum is clearly not an unbiased estimator of the population maximum, as shown by Equation (4).The bias in the sample maximum $X_{(n)}$ is given by

$$bias\left[X_{(n)}\right] = N - E\left[X_{(n)}\right]$$

$$= \frac{N-n}{n+1} \qquad (5)$$

Now, the sampling variance of the sample maximum is obtained by obtaining the second raw moment of the sample maximum. For this, consider the factorial moment

$$E\left[X_{(n)}\left(X_{(n)}+1\right)\right] = \sum_{r=n}^{N} r(r+1)P\left[X_{(n)} = r\right]$$

$$= \sum_{r=n}^{N} r(r+1).\, \frac{\binom{r-1}{n-1}}{\binom{N}{n}}$$

$$= \frac{1}{\binom{N}{n}} \sum_{r=n}^{N} r(r+1).\, \binom{r-1}{n-1}$$

$$= \frac{1}{\binom{N}{n}} \sum_{r=n}^{N} \frac{(r+1)!}{(n-1)!(r-n)!}$$

$$= \frac{n(n+1)}{\binom{N}{n}} \sum_{r=n}^{N} \frac{(r+1)!}{(n+1)!(r-n)!}$$

$$= \frac{n(n+1)}{\binom{N}{n}} \binom{N+2}{n+2}$$

$$= n(n+1).\frac{n!(N-n)!}{N!} \cdot \frac{(N+2)!}{(n+2)!(N-n)!}$$

$$= n(n+1).\frac{(N+1)(N+2)}{(n+1)(n+2)}$$

$$= \frac{(N+1)(N+2)}{(n+2)}.n \qquad (6)$$

The second raw moment of the sample maximum is then obtained by using the following relationship

$$E\left[X_{(n)}^2\right] = E\left[X_{(n)}\left(X_{(n)}+1\right)\right] - E\left[X_{(n)}\right] \quad (7)$$

From Equation (4) and (6)

$$E\left[X_{(n)}^2\right] = \frac{(N+1)(N+2)}{n+2}\pi - \frac{N+1}{n+1}\pi$$

$$= \frac{(N+1)(nN+N+n)}{(n+1)(n+2)}\pi \quad (8)$$

Finally, we obtain the sampling variance of the sample maximum as

$$Var\left[X_{(n)}\right] = E\left[X_{(n)}^2\right] - \left\{E\left[X_n\right]\right\}^2$$

$$= \frac{(N+1)(nN+N+n)}{(n+1)(n+2)}n - \frac{(N+1)^2}{(n+1)^2}\pi^2$$

$$= \frac{(N+1)(N-n)}{(n+1)^2(n+2)}\pi \quad (9)$$

Since $X_{(n)}$ is not unbiased for the population maximum its mean squared error is obtained as

$$MSE\left[X_{(n)}\right] = Var\left[X_{(n)}\right] + \left\{bias\left[X_n\right]\right\}^2$$

$$= \frac{(N+1)(N-n)}{(n+1)^2(n+2)}n + \frac{(N-n)^2}{(n+1)^2}$$

$$= \frac{(N-n)(2N-n)}{(n+1)(n+2)} \quad (10)$$

Estimation of Population Maximum under Stratified Random Sampling

When the goal of sampling is to estimate the population maximum, stratified random sampling may not be the best option because, in its most frequent form, it aims to acquire comprehensive data on a heterogeneous population without increasing the sample size unnecessarily. When the goal is to estimate the population maximum, however, only one stratum can give the essential information. As a result, only one stratum should be sampled, with all other strata and sampling units in those strata being ignored.

Suppose size of population is N, k is the number of strata and N_1, N_2, ...,N_k are stratum sizes. For h = 1,2,..., k, the stratum boundaries are denoted by x_{h_l} (l for lower boundary) and x_{h_u} (u for upper boundary). Without loss of generality suppose further that strata are numbered in such a way that $x_{h_u} = x_{(h+1)}$ for h = 1, 2, ..., k -1. It is then obvious that the first k - 1 strata cannot contain the population maximum, and that the sample must therefore be drawn only from stratum number k. Let us denote its size by S, so that the largest value among the N_k sampling units in the stratum by selecting a sample using SRSWOR of size n_k from the stratum.

It may be easy to understand the situation if it is described as follows. The sampling units in the population are arranged in an ascending order, so that strata are non-overlapping. The k strata can be represented as follows.

If the problem is described as follows, it may be easier to comprehend. The population's sampling units are grouped in ascending order to prevent strata from overlapping. The k strata are represented in the following way.

$$\text{Stratum 1} = \left\{x(1), x(2), x(3), \ldots, x(N_1)\right\},$$

$$\text{Stratum 2} = \left\{x(N_1+1), x(N_1+2), \ldots, x(N_1+N_2),\right\},$$

$$\vdots$$

$$\text{Stratum k} = \left\{x(N-N_k+1), x(N-N_k+2), \ldots, x(N)\right\}.$$

However, none of these values are unknown in practice. The above representation can be simplified even more using Equation (4.1), resulting in the following representation.

unbiased estimator of population mean under stratified sampling whereas the sample maximum is not an unbiased estimator of population maximum under simple random sampling and stratified sampling. When the goal of sampling is to estimate the population maximum, stratified random sampling may not be the best option because, in its most frequent form, it aims to acquire comprehensive data on a heterogeneous population without increasing the sample size unnecessarily. When the goal is to estimate the population maximum, however, only one stratum can give the essential information. As a result, only one stratum should be sampled, with all other strata and sampling units in those strata being ignored. But when the goal is to estimate the population mean, all strata gives the essential information. As a result, all strata should be sampled to estimate population mean.

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Design, synthesis of anticancer and anti-inflammatory 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio) pyrimidine-5-carbonitriles

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ABSTRACT

A novel series of 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio) pyrimidine-5-carbonitriles (**4a–i**) was synthesized and evaluated for anticancer potential against cell lines for breast cancer. Compounds **4b**, **4e**, and **4h** exhibited prominent cytotoxicity against human breast carcinoma MCF-7 cell line with GI_{50} of 2.0, 0.5, and 0.5 μM, respectively. Molecular docking study against EGFR tyrosine kinase could provide valuable insights into the plausible mechanism of action. The compounds could bind with significantly high binding affinity and their binding affinity scores could correlate well with the observed anticancer activity. Furthermore, compounds **4a**, **4c**, **4e**, **4g**, and **4i** exhibited significant inflammatory activities as well which could expand the therapeutic domain of this novel series.

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Introduction

Cancer is one of the major causes of mortality worldwide. Literature reports 10.0 million deaths and around 19.1 million new cases just in 2020.[1] Perhaps the cancer frequency will augment by above 30% in the forthcoming decades. Compared to all other types of cancer, breast cancer is communal hostile with an assessed 2.3 million new cases.[2–4] Presently for breast cancer treatment numerous therapy are existing, such as surgery, radiotherapy, teletherapy, chemotherapy, and nanotechnology techniques however, these tactics have some confines.[5,6] In recent decades cellular pathways and specific biomolecular inhibition strategies have immense significant targets in cancer therapy.[7,8] Henceforth there is a stipulation to find the anticancer compounds, which

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could act upon the multiple target site into the cancer cell.[9] Earlier reports suggested that the scaffolds anticancer compounds enhanced the exploration for probable biomolecular targets into the cancer cells.[10–12]

Body physiological response to tissue injury is inflammation, it is because of infection, physical damage, and toxin contact.[13] Chronic inflammation may lead to various diseases, such as arthritis, Alzheimer, cancer, and autoimmune disease.[14,15] Inflammatory cells have a prevailing influence on the development of the tumor, which promotes angiogenesis, and creates a favorable condition for tumor growth early in the neoplastic processes.[16] Hence for cancer preclusion and treatment targeting inflammation is one of the tactics.[17]

Long-before indole nucleus received substantial focus due to its bioactivities, such as anti-microbial,[18] anti-rheumatoid, anti-inflammatory, antioxidant, antipyretic, anticonvulsant, antidiabetic, antimalarial, analgesic, anticancer, and selective inhibitor of COX-2.[19–21,22] Literature review suggested that indole derivatives were excellent anticancer agents and induced apoptosis in pancreatic, colon, cervical, squamous cell carcinoma, prostate, and breast cancer cell lines.[23–27]

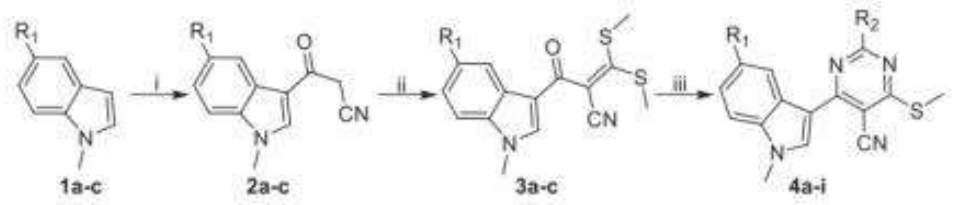
Pyrimidine is an aromatic heterocyclic compound having wide existence in nature, which is present in uracil, thymine, cytosine DNA bases, and isolated from terrestrial as well as marine plants.[28–30] Pyrimidine and its natural, as well as semisynthetic derivatives, were reported to have a broad range of pharmacological activities, such as antidiabetic, anti-inflammatory, anti-HIV, antimicrobial, anti-tubercular, cardiovascular, antioxidant, analgesic, diuretic, and anticancer.[31–34] Compared to all other bioactivities, the anticancer activity of pyrimidine and its derivatives were studied extensively. It is a potential anticancer skeleton, which showed cytotoxicity against a range of cancerous cell lines.[35–37] Pyrimidines-based molecules were reported to demonstrate the most significant cytotoxicity against breast carcinoma amongst all other cancer cell lines (Fig. 1).[38–40]

Chemical hybridization leading to the blending of multiple scaffolds is one of the effective strategies for drug discovery, to enhance the bioactivity of individual molecules.[41–44] With this objective, we have synthesized indol-pyrimidine scaffolds, as cytotoxic and anti-inflammatory agents. Moreover, the in-silico approach of molecular docking was adopted to gain an insight into their plausible anticancer activity for which Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase was used as the target protein. Furthermore, these compounds were also evaluated for potential anti-inflammatory activity.

Result and discussion

Synthesis and characterization of 4-(1-methyl-1H-indol-3-yl)-6-(methylthio) pyrimidine-5-carbonitriles (4a–i)

In the present study, we have achieved the synthesis of the desired 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio)pyrimidine-5-carbonitriles (**4a–i**) starting from substituted 1-methyl-1*H*-indoles by chemo and regioselective cyclization in a few steps with excellent yield. Initially, 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanenitriles (**2a–c**) were synthesized by cyano acetylation of substituted (–CN, $-OCH_3$) 1-methyl-1*H*-indoles (**1a–c**)using 2-



	R_1	R_2
4a	H	NH_2
4b	CN	NH_2
4c	OCH_3	NH_2
4d	H	CH_3
4e	CN	CH_3
4f	OCH_3	CH_3
4g	H	Ph
4h	CN	Ph
4i	OCH_3	Ph

Scheme 1. Synthesis of 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio)pyrimidine-5-carbonitriles.

cyanoacetic acid in acetic anhydride under reflux conditions.[45] Then, 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanenitriles (**2a–c**) on reaction with carbon disulfide in the presence of sodium tert-butoxide followed by alkylation with dimethyl sulfate converted to 2-(1-methyl-1*H*-indole-3-carbonyl)-3,3-bis(methylthio)acrylonitriles (**3a–c**).[46,47] Further, 2-(1-methyl-1*H*-indole-3-carbonyl)-3,3-bis(methylthio)acrylonitriles (**3a–c**) on cycloaddition with substituted guanidine hydrochloride under an alkaline condition in acetonitrile furnished desired 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio) pyrimidine-5-carbonitriles (**4a–i**) (Scheme 1). The products obtained were purified using the column chromatographiy using ethyl acetate in hexane. All the synthesized compounds were characterized by infrared (IR) , high-resolution mass spectrum (HRMS), proton, and carbon NMR spectra.

Anticancer activity

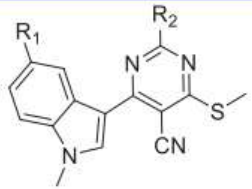
All the synthesized target molecules (**4a–i**) were screened for their anticancer potential against MCF-7, a human breast cancer cell line. The VERO African green monkey kidney epithelial cell lines were used as a control. The cytotoxicity was measured by determining the GI_{50}, TGI, and LC_{50} values, and adriamycin was treated as a positive control (Table 1). GI_{50} is a drug concentration that causes a 50% reduction in cell proliferation whereas the concentration required to kill test cells by 50% was stated as lethal concentration (LC_{50}) and cells total growth inhibition of was denoted TGI.

Among the compounds screened, **4b**, **4e**, and **4h** are found to be more potent in total growth inhibition concentration studies than other 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio)pyrimidine-5-carbonitriles. Results revealed that compound **4b**, **4e**, and **4h** have cyano group at C-5 position. Indol ring play a significant role in the activity due to which the molecule could snuggly fit into the active site of EGFR tyrosine kinase with a significantly higher binding affinity.

Compound **4h** and **4b** exhibited cytotoxicity with TGI values of 50 and 60%, respectively. 4-(1-Methyl-1*H*-indol-3-yl)-6-(methylthio)pyrimidine-5-carbonitriles derivatives (**4a**, **4c**, **4d**, **4f**, **4g**, **4i**) disclosed poor activity as compared to the adriamycin. Compound **4e**, **4h**, and **4b** revealed significant cytotoxicity with 50% cell growth inhibition at 0.5, 0.5, and 2.0 μM concentrations, respectively.

The lethal concentration studies indicated that all the compounds were found non-toxic. In total growth inhibition concentration studies except for **4e** (39.3 μM), other synthetic derivatives were found non-toxic against VERO cells. *In vitro* cytotoxicity

Table 1. *In vitro* anticancer screening of indole-pyrimidine scaffolds (**4a–i**) against human breast cancer cell line MCF-7[a] and normal monkey cell line VERO.



			MCF-7 (μM)		VERO (μM)						
Comp.	R_1	R_2	GI_{50}[d]	TGI[c]	LC_{50}[b]	GI_{50}	TGI	LC_{50}	Glide Score	Glide energy (Kcal/mol)	H-bond (Å)
4a	H	NH_2	>100	>100	>100	>100	>100	>100	−7.564	−38.956	Asp831 (2.209), Lys721 (2.167), Thr766 (2.177)
4b	CN	NH_2	**2.0**	**60.0**	>100	2.0	>100	>100	−8.119	−45.169	Asp831 (2.184), Lys721 (2.236), Thr766 (2.058)
4c	OCH_3	NH_2	>100	>100	>100	>100	>100	>100	−7.504	−38.102	Asp831 (2.033), Lys721 (2.469), Thr766 (2.276)
4d	H	CH_3	>100	>100	>100	40.0	>100	>100	−7.823	−39.031	Lys721 (2.141), Thr766 (2.126)
4e	CN	CH_3	**0.5**	**99.0**	>100	2.0	39.3	>100	−8.211	−47.343	Lys721 (2.543), Thr766 (2.266)
4f	OCH_3	CH_3	>100	>100	>100	>100	>100	>100	−7.224	−37.764	Lys721 (2.441), Thr766 (2.206)
4g	H	Ph	>100	>100	>100	>100	>100	>100	−7.194	−37.223	Lys721 (2.301), Thr766 (1.867)
4h	CN	Ph	**0.5**	**50.0**	>100	7.0	>100	>100	−8.228	−47.478	Lys721 (2.660), Thr766 (2.281)
4i	OCH_3	Ph	>100	>100	>100	>100	>100	>100	−7.089	−37.286	Lys721 (2.633), Thr766 (2.388)
Adriamycin			< 0.1	40.0	>100	<0.1	10.0	>100	−8.558	−55.564	Asp776 (2.487), Asp831 (1.916)

[a]Concentrations in μM.
[b]Concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) calculated from $[(Ti - Tz)/Tz] \times 100 = -50$.
[c]Drug concentration resulting in total growth inhibition (TGI) was calculated from $Ti = Tz$.
[d]Growth inhibition of 50% (GI_{50}) calculated from $[(Ti - Tz)/(C - Tz)] \times 100 = 50$.

studies indicated that **4b**, **4e** exhibited moderate cytotoxicity against VERO cell line with 2.0 μM GI_{50} values. Compound **4b** (GI_{50} 7.0 μM) showed low cytotoxicity, whereas derivatives **4a**, **4c**, **4d**, **4f**, **4g**, and **4i** are non-cytotoxic ($GI_{50} > 100$ μM) against VERO cell line.

Molecular docking

To gain mechanistic insight into the anticancer activity demonstrated by 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio)pyrimidine-5-carbonitriles (**4a–i**) investigated herein, a molecular docking study was performed against a crucial target intervening the breast cancer pathophysiology, epidermal growth factor receptor (EGFR) tyrosine kinase. Amplification or over-expression of this target has been associated with the development and progression of certain destructive types of breast cancer. Specifically, the aberrant activity of EGFR has shown to play a major role in the development and growth of tumor cells, where it is involved in numerous cellular responses including proliferation, signaling, differentiation, adhesion, migration, and survival of cancer cells. With this objective, the crystal structure of Epidermal Growth Factor Receptor Tyrosine Kinase in complex with its inhibitor was retrieved from the protein data bank (PDB) (PDB code: 1M17) and subjected to molecular docking using the standard protocol implemented in the Glide (Grid-Based Ligand Docking With Energetics) program[48,49] integrated into the Schrödinger molecular modeling package (Schrödinger, LLC, New York, NY, USA, 2018) (detail protocol is described in the Experimental section).

The in-silico binding affinity study could yield crucial information concerning the orientation of the 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio)pyrimidine-5-carbonitriles (**4a–i**) in the binding pocket of the EGFR tyrosine kinase protein. Their docking scores and the binding energy values corroborated well with the experimental anticancer potency showing a significant correlation, with an average docking score of −7.622 and Glide binding energy −40.602 kcal/mol (Table 1). Visual inspection of the binding poses indicates that these indole-pyrimidine scaffolds (Fig. 2, Figs. S5a–l) could accommodate well within the active site of EGFR tyrosine kinase protein, and the complex formed with the target enzyme was stabilized through a network of significant bonded and non-bonded interactions. A detailed analysis of the ligand-receptor interaction is elaborated for one of the most active analogs **4h** in the next section and could be visualized pictorially through Figures S5a–i for the remaining molecules in the series.

The lowest energy docked conformation of **4h** (Fig. 2) showed that the molecule could snuggly fit into the active site of EGFR tyrosine kinase with a significantly higher binding affinity (docking score of −8.228 and Glide binding energy −47.478 kcal/mol) engaging in a network of bonded and non-bonded interactions with the surrounding residues. A detail insight into the per-residue interactions revealed that the molecule could establish a network of significant van der Waals interactions with Asp831 (−4.187 kcal/mol), Thr830 (−2.119 kcal/mol), Thr766 (−1.295 kcal/mol), Leu764 (−2.169 kcal/mol), Met742 (−1.143 kcal/mol), Glu738 (−1.365 kcal/mol), Lys721 (−4.427 kcal/mol), Ile720 (−1.022 kcal/mol), Ala719 (−1.498 kcal/mol), and Phe699 (−2.689 kcal/mol) through the 3-(5-cyano-6-(methylthio)-2-phenylpyrimidin-4-yl)-1-methyl component while the 1H-indole-5-carbonitrile portion exhibited similar type of

interactions with Leu820 (−3.615 kcal/mol), Cys773 (−1.166 kcal/mol), Gly772 (−1.474 kcal/mol), Pro770 (−1.781 kcal/mol), Met769 (−2.098 kcal/mol), Leu768 (−2.564 kcal/mol), Val702 (−4.647 kcal/mol), Gly695 (−1.101 kcal/mol), Leu694 (−3.924 kcal/mol) lining the active site. The enhanced binding affinity of **4h** is also attributed to favorable electrostatic interactions observed with Asp831 (−1.2 kcal/mol), Lys828 (−1.261 kcal/mol), Met769 (−1.941 kcal/mol), Gln767 (−1.234 kcal/mol), Thr766 (−1.125 kcal/mol), Glu738 (−1.106 kcal/mol), and Lys721 (−3.099 kcal/mol) residues. Furthermore, two prominent hydrogen bonding interactions were also observed through pyrimidine nitrogen with Lys721 (2.660 Å) and the second with Thr766 (2.281 Å) through the nitrile function. Such hydrogen bonding interactions "anchor" the ligand to the active site of the enzyme and facilitate the steric and electrostatic interactions adding to the stability of the enzyme-inhibitor complex. Interesting introduction of a functional

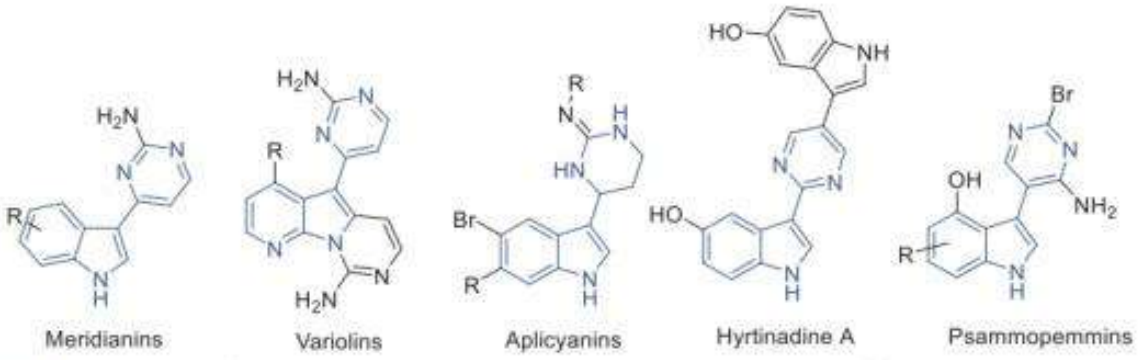


Figure 1. Structure of bioactive natural products with indolyl-pyrimidine scaffolds.

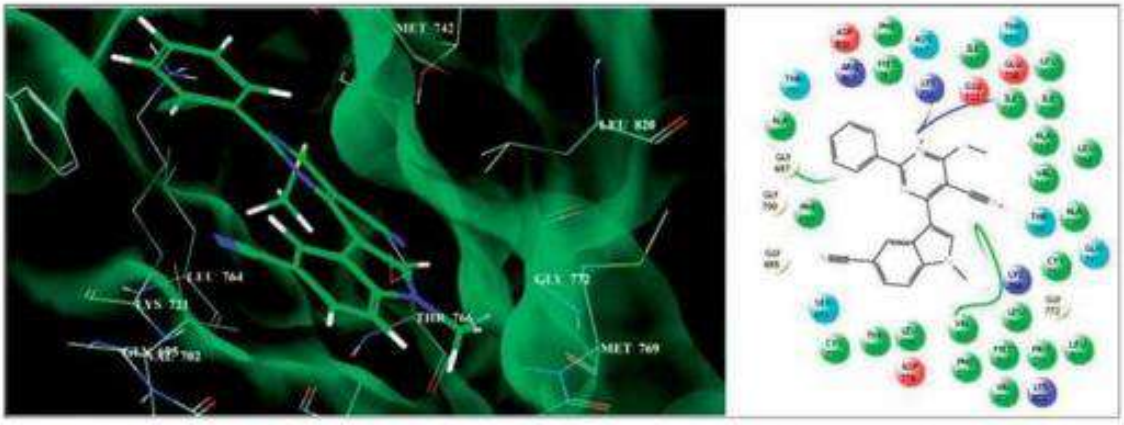


Figure 2. Binding mode of compound **4h** into the active site of EGFR tyrosine kinase (On the right side: pink lines indicate hydrogen-bonding interactions).

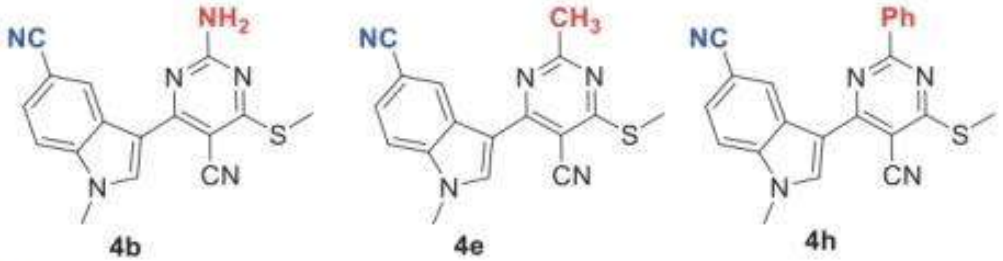


Figure 3. Active anticancer 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio)pyrimidine-5-carbonitriles.

group capable of engaging in hydrogen bonding at the R2 position of the pyrimidine ring *viz.* **4a**, **4b**, and **4c** (NH_2) resulted in an additional hydrogen bond through Asp831 residue which was missed in case of molecules lacking such group *viz.* **4d–4i**. A similar network of bonded and non-bonded interactions was established by other molecules in the series which served as the primary driving forces for mechanical interlocking of these molecules into the active site of EGFR tyrosine kinase. This information derived from this analysis is now being fruitfully utilized for the point-specific mutation around the scaffold to identify molecules with higher binding affinity and potency toward EGFR Tyrosine Kinase. 4b, 4e, and 4h (Fig. 3) more anticancer potential compared to other screened compounds in molecular docking and TGI concentration studies.

Heat-induced protein denaturation

As the protein's denaturation is a well-studied cause for inflammation.Therefore, *in vitro* anti-inflammatory activity of synthesized compouds (**4a-i**) was evaluated by using egg albumin denaturation method (Table 2). The results of anti-inflammatory screening reveal that compounds **4d**, **4e**, and **4g** displayed substantial inhibition (76.25, 80.72 and 75.10%, respectively) at 1mM concentration, compared to the positive control diclofenac sodium (90.21%). All other derivatives displayed moderate inhibition of heat-induced albumin denaturation (68.70–73.12%) except compounds **4a** and **4b** compared to the reference standard.

Antioxidant activity

It is well-documented that free radicals, such as the reactive oxygen species (ROS) are important in the pathophysiological mechanisms related to several inflammatory disorders. These free radicals were interacting with cell biomolecules, which may affect the normal physiological functions of the cells and may lead to cancer. Free radical scavenging is possible by using antioxidant therapy, which is one of the current options. Hence, we have tested all the synthetic derivatives to study their direct scavenging potential against various sensitive oxygen and nitrogen radicals, such as nitric oxide (NO), 2,2-diphenyl-2-picrylhydrazyl (DPPH), and superoxide (SOR). The results presented in Table 3indicates that most of the derivatives exhibited good to excellent activity. Utmost all the synthetic analogs exhibited substantial NO and SOR scavenging activity except **4b**

Table 2. Effect of 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio)pyrimidine-5-carbonitriles (**4a–i**) on heat-induced protein denaturation.

Entry	% inhibition (1 mM)
4a	64.37 ± 1.10
4b	56.62 ± 2.06
4c	76.25 ± 0.08
4d	73.12 ± 2.13
4e	80.72 ± 0.15
4f	71.87 ± 0.03
4g	75.10 ± 1.07
4h	68.67 ± 2.16
4i	71.80 ± 3.05
Diclofenac sodium	90.21 ± 1.75

Table 3. *In vitro* anti-oxidant activity of 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio)pyrimidine-5-carbonitriles (**4a–i**).

	% inhibition (1mM)			
Entry	DPPH	NO	SOR	H_2O_2
4a	52.94 ± 1.18	67.21 ± 0.62	83.73 ± 0.43	34.31 ± 1.75
4b	30.63 ± 0.23	35.89 ± 1.44	65.85 ± 2.56	39.35 ± 0.54
4c	45.29 ± 2.50	54.91 ± 0.37	95.93 ± 0.78	29.82 ± 2.64
4d	29.41 ± 0.68	64.75 ± 0.66	92.90 ± 2.85	24.95 ± 0.13
4e	30.90 ± 1.24	61.53 ± 0.45	82.92 ± 1.16	42.91 ± 3.78
4f	47.05 ± 1.45	37.70 ± 2.13	88.61 ± 4.45	24.95 ± 0.83
4g	35.29 ± 0.38	68.03 ± 1.38	74.79 ± 1.90	25.53 ± 0.91
4h	36.36 ± 1.10	62.82 ± 0.53	75.60 ± 0.67	45.75 ± 1.22
4i	44.70 ± 0.79	62.29 ± 4.87	76.92 ± 3.48	29.62 ± 2.61
AA	44.18 ± 0.54	42.63 ± 1.22	74.07 ± 2.89	47.17 ± 0.42

AA: Ascorbic acid (at 15 µg/mL); data represent mean of two replicates.

and **4f**. Compounds **4a**, **4d–f**, **4g–h**, **4i** showed greater inhibition of NO radicals (>54.91%) compared to the positive control ascorbic acid (42.63%). However, only **4b** and **4f** showed poor activity with 35.89 and 37.70% inhibition, respectively. Compounds **4a**, **4d–h**, **4i** showed significant SOR scavenging activity with >74.79% inhibition compared to the standard drug ascorbic acid (74.07%). However, **4b** displayed moderate SOR scavenging activity. DPPH scavenging activity results suggested that only a few derivatives were found to be more active, **4a** (52.94%), **4c** (45.29%), **4f** (47.05%), and **4i** (44.70%) compared to the ascorbic acid (44.18%). The results of H_2O_2 radical scavenging studies showed that except compounds **4e** and **4h** all other derivatives were inactive compared to the ascorbic acid.

Conclusion

In conclusion, new 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio) pyrimidine-5-carbonitriles **4a-i** were synthesized with excellent yield (90–96%). All the synthesized compounds exhibited potent anticancer activity against breast cancer cell line, which was significantly altered with the substitution of indole and pyrimidine. Compounds **4b**, **4e**, and **4h** showed prominent cytotoxicity against MCF-7, whereas these derivatives exhibited weak cytotoxicity against normal VERO cell line. Furthermore, molecular docking study could provide valuable mechanistic insight of the binding mode and affinity toward EGFR tyrosine kinase which is a crucial target intervening in breast carcinoma. In addition, compound **4e** was found to be an effective anti-inflammatory agent and **4a**, **4c**, and **4i** were exhibited potential DPPH , NO, and SOR radical scavenging activity. This synthetic approach can be explored for the synthesis of new indole-pyrimidine based anticancer drugs.

Experimental

General procedure for the preparation of 2-(1-methyl-1H-indole-3-carbonyl)-3,3-bis(methylthio)acrylonitrile (3a–c)

To a stirred suspension of freshly prepared sodium *tert*-butoxide (3.0 mmol) in dry THF (7 mL) at 0 °C, a solution of substituted 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanenitrile (1.0 mmol) and carbon disulfide (1.2 mmol) in dry THF (5 mL) was added

through a pressure equalizer funnel, and the mixture was vigorously stirred at 0 °C for 1 h. To this suspension, a solution of dimethyl sulfate (1.2 mmol) in dry THF (5 mL) was carefully added dropwise during 10 min at 0 °C, and the reaction mixture was allowed to stir at 0 °C for 1 h. After completion of the reaction (TLC; hexane/EtOAc, 8:2), the mixture was diluted with ice water. A light-yellow solid was collected with filtration followed by water washing. The crude solid was purified by recrystallization with ethanol or dichloromethane-hexane mixture.

General procedure for the synthesis of indole-pyrimidine scaffolds (4a–i)

A mixture of 2-(1-methyl-1*H*-indole-3-carbonyl)-3,3-bis(methylthio)acrylonitrile **3a–d** (1.0 mmol), guanidine hydrochloride (1.2 mmol), anhydrous K_2CO_3 (1.5 mmol), and acetonitrile (10 mL) was heated at reflux for 12 h. After cooling, the reaction mixture was poured into ice water. The white solid obtained was filtered, washed with water, and recrystallized from ethanol to obtain pure compound **4a–i**.

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Disclosure statement

The authors declare no competing interests.

Ethical approval

All authors have agreed on the final version of this paper.

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REVIEW ARTICLE

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Biocatalytic transformations of bioactive labdane diterpenoids from *Andrographis paniculata* (Burm f.) Nees: A review

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ABSTRACT

Medicinally active labdane diterpene lactones, andrographolide (**1**), neoandrographolide (**2**), dehydroandrographolide (**3**) and deoxyandrographolide (**4**) are isolated from medicinal plant, *Andrographis paniculata*. These diterpenes have many beneficial health effects such as anti-viral, anti-inflammatory, anti-cancer and anti-diabetes. However, to improve bioactivity and water solubility, analogues of labdene diterpenes have been synthesised using synthetic and biotransformation routes. Biocatalytic modification has extensive potential for the preparation of a wide variety of complex, structurally diverse and more potent organic compounds at milder and eco-friendly reaction conditions. Therefore, it is necessary to systematically accumulate the biotransformation reports for isolated lactones. This article reviews the regioselective transformations of bioactive labdane diterpenes isolated from *Andrographis paniculata*. The whole-cell and pure enzymatic transformations of andrographolide (**1**) and its derivatives are presented concisely.

GRAPHICAL ABSTRACT

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Biocatalysis; fungi; lipases; andrographolide; microbial; labdane diterpenoids

1. Introduction

Andrographis paniculata is a medicinally important plant that belongs to Acanthaeceae family and traditionally known for the treatment of diseases such as cancer, ulcer, diabetes, dysentery, malaria, skin diseases and high blood pressure (Rajagopal et al. 2003). Labdane diterpenes isolated from different parts of *A. paniculata* such as andrographolide (**1**), neoandrographolide (**2**), dehydroandrographolide (14-deoxy-11,12-didehydroandrographolide) (**3**) and deoxyandrographolide (14-deoxy-didehydroandrographolide) (**4**) are responsible for medicinal properties of the plant (Figure 1). These diterpenes in pure form also exhibits vast array of pharmaceutical activities such as anti-inflammatory, anti-cancer and anti-diabetes (Levita et al. 2010; Sivakumar and Rajeshkumar 2016). Andrographolide (**1**) is very useful in arresting viral infections, plays an important role in the treatment of colitis and also shown to inhibit atherosclerosis and suppress skin diseases (Michelsen et al. 2013; Shao et al. 2016; Gupta et al. 2017). Andrographolide (**1**) has bioactive skeleton with six stereocenters, primary, secondary and allylic hydroxy groups at C-19, C-3 and C-14 positions, respectively. It also consists of a sensitive lactonic ring existing in twisted conformation, exocyclic double bond and E-configuration of γ-lactone bridge (Aromdee 2012). The structure-activity relationship analysis of **1** and its derivatives have shown that the existing hydroxy groups, lactone moiety and conjugated double bond are core functional groups responsible for specific activities (Dai et al. 2019). Despite of various known biological activities, further development of structurally modified derivatives with increased efficacy, stability, solubility and decreased toxicity is desirable to improve clinical applications of major metabolites isolated from *Andrographis paniculata*.

One of the commonly accepted approaches to improve the biological and medicinal properties of previously known active entities is structural modifications (Ameenah 2006). Chemical methods of modification have been traditionally used for the synthesis of medicinally important derivatives. However, chemical synthesis has limitations for stereoselective reactions and involves several protection and de-protection steps. This lead to low yield, environmental pollution as well as increases cost of the process. On the other hand, biocatalysis is an alternative – "green" and environment friendly approach which can efficiently

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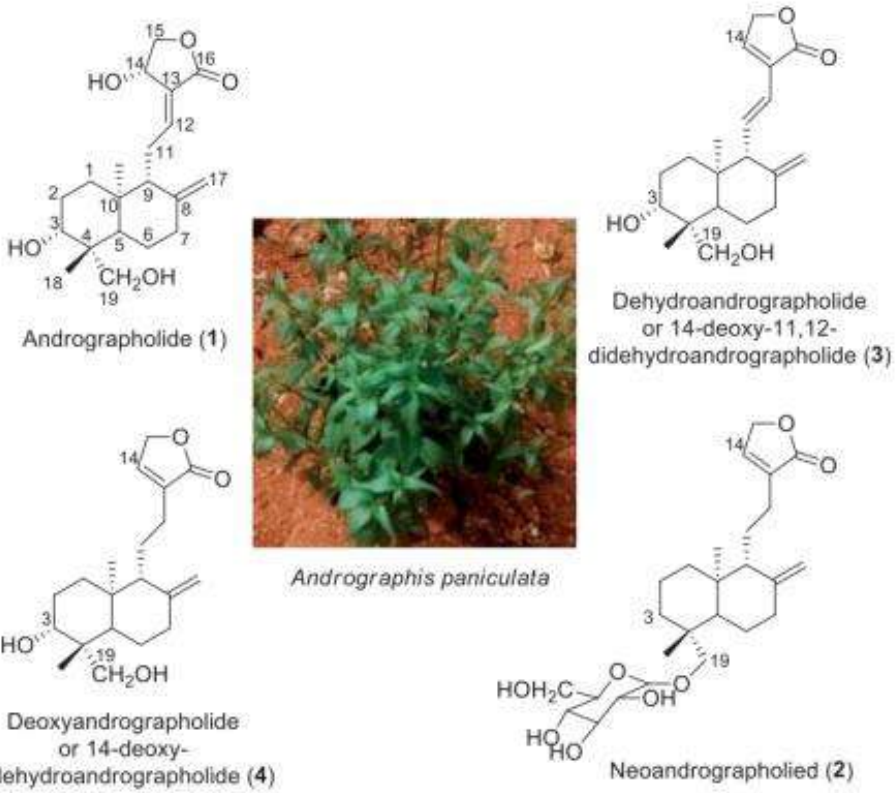


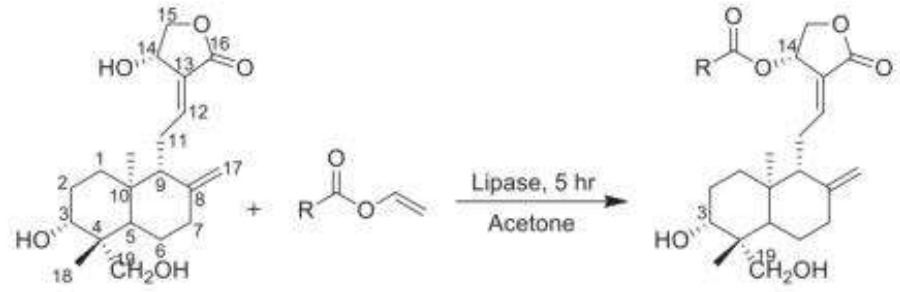
Figure 1. Diterpene lactones isolated from *Andrographis paniculata* (Burm f.) Nees.

substitute reagents based synthetic methods. Biocatalytic derivatization offers regio- as well as stereoselective functionalization of complex and sensitive molecules (Clouthier and Pelletier 2012; Haldar et al. 2013). Biotransformation reactions proceed under mild conditions, do not generate toxic byproducts and have ability to modify carbon atoms difficult to be functionalized. In addition, biocatalytically modified active molecules are considered as of "natural" origin (Bicas et al. 2009). Consequently, the importance and demand of the biochemical approach is increasing at high rate. Biocatalytic modifications of compounds can be achieved by fermentation using whole-cell microorganisms like bacteria, fungi, yeast as well as purified enzymes from different classes such as lipases (Fern'Andez et al. 2006; Kumar et al. 2016; Sharma et al. 2016). Therefore, use of purified enzymes and microbial cells for the transformation of natural products is well studied.

Few groups of scientists have explored microbial lipases extracted from bacteria, yeast and fungi for the regio- and stereo- selective functionalization of andrographolide (**1**). Further, reports are available elucidating the use of fungal cultures such as *C. blakesleeana, A. ochraceus, A. Niger, R. stolonifier, M. spinosus, C. elegans* and *F. graminearum* for whole cell transformation of isolated diterpene lactones into hydroxylated, reduced and oxidised derivatives. This review summarizes altogether the biochemical modifications of medicinally active labdane diterpenoid lactones isolated from *Andrographis paniculata* with respect to the nature of biocatalytic reactions, experimental conditions, transformation products and structure-activity relationship studies. A couple of review articles based on biocatalytic modifications of labdane diterpenes are known in the literature. However, they have not included the diterpene lactones isolated from *Andrographis paniculata* or discussed the biotransformation reports from previous decade (Frija et al. 2011; Wang et al. 2013).

2. Enzyme catalyzed transformations

The hydroxy groups existing in andrographolide (**1**) have considerable impact on its biological activities and a significant enhancement in activities has been observed on individual modification of these groups (Fern'Andez et al. 2006). Selective modifications of hydroxyl groups in **1** are difficult using synthetic routes due to their similar reactivity and presence of sensitive lactone ring. However, the transformation potential of enzymes, specifically lipases has been explored extensively for regio and stereo-selective modification of hydroxyl groups in complex substrates.



Scheme 1. Lipase catalysed transformation of andrographolide (**1**).

Table 1. Acylation of **1** at C-14 hydroxyl with vinyl acetate catalysed by various enzymes.

Entry	Enzyme	Source	Conversion (%) (Chen et al. 2009)
1	Novozym 435	*Candida Antarctica* type B	99.5
2	Lipozyme^{IM} TL	*Thermomyces lanuginosus*	51.0
3	Lipozyme^{IM} RM	*Rhizomucor miehei*	23.3
4	Lipozyme^{IM}	*Mucor miehei*	18.1
5	Lipase AH	*Pseudomonas cepacia*	19.0

Accordingly, various microbial lipases have been used for acylation of hydroxyl group specifically at C-14 positions of **1** using different acyl donors (Scheme 1).

For the first time, Chen et al. (2009) have developed a highly efficient and lipase mediated bioconversion process of andrographolide (**1**) to 14-*O*-acetylandrographalide (**5**). Various commercially available lipases and proteases were screened for regioselective acylation of **1** using vinyl acetate as an acyl donor. The transformation reaction was carried out in acetone at 45 °C with vinyl acetate. Out of the screened enzymes, four enzymes namely Novozym 435, Lipozyme TL, Lipozyme^{IM} RM, Lipozyme^{IM} have shown monoacetylation activity, Table 1. Maximum conversion (99%) and highest yield (96.5%) was obtained with immobilized lipase from *Candida Antarctica* (Novozyme 435), however, proteases were unable to show desired activity. Further, the same group reported exclusive monoesterification of **1** at C-14 position using PSL-C an immobilized lipase from *Burkholderia cepacia* (Chen et al. 2010). The effect of different factors such as water activity, reaction temperature and time on bioconversion of **1** was investigated. It was depicted that the performance of acylation reaction in acetone depends on water activity. Maximum substrate conversion was observed with 0.11 water activity. The thermal stability of the enzyme was evaluated in the temperature range from 30 to 70 °C and maximum production of 14-acetyl andrographolide was observed at 45–50 °C. Time course experiment indicated that 99.0% substrate conversion was obtained on incubation of **1** with PSL-C for the period of 4 hrs under standardized reaction conditions. The investigation of reusability of PSL-C enzyme for industrial production revealed that PSL-C could be used at least five times without significant loss in enzyme activity. In the extension studies, immobilized *Candida antartica* lipase B (Novozym 435) and Amano lipase AK (P. fluorescens) enzymes along with different acyl moieties were used for the production of series of 14-substituted andrographolide derivates, Table 2 (Chen et al. 2011). The scale up and operational stability experiments revealed that Novozym 435 could be recycled for the production of 14-acylated andrographolide derivatives on 35 gram scale for 8 batches while maintaining 77-92% of its original activity. The structure-activity study of the obtained derivatives against Gram-positive and Gram-negative bacteria evaluated that there is a significant effect of acyl moiety on the antibacterial activity. The strongest activity was shown by 14-butyryl andrographolide against the Gram-positive bacterium *B. cereus* and Gram-negative *E.coli*.

Different combinations of lipases and acyl donors have been screened for the transformation of **1** (Patil et al. (2018). The focus of the study was monoesterification of **1** specifically at C-14 position using different acyl donors. Out of the studied enzymes, Amano lipase AK (*P. fluorescens*) was able to transfer selected acyl groups such as acetate, propionate, butyrate, decanoate and laurate to the hydroxyl group at C-14 position of **1**, Table 2. Further, the kinetic study of esterification with respect to solvent for reaction, temperature, chain length of acyl donors and incubation period up to 6 hrs revealed the optimal conditions for monoesterification of andrographolide (**1**) using

Table 2. Effect of acyl donor chain length on the regioselective acylation of **1**.

Entry	Acyl Donar	Conversion (%)	
		Novozym 435[a] (Chen et al. 2011)	Amano lipase AK (P. fluorescens)[b], (Patil et al. 2018)
1	Vinyl acetate	92.2	98.2
2	Vinyl propionate	nd[c]	98.5
3	Vinyl butyrate	90.4	96.3
4	Vinyl octanoate	88.2	nd
5	Vinyl decanoate	nd	95.6
6	Vinyl laurate	86.7	94.5
7	Vinyl stearate	79.4	nd

[a]The reaction conditions: 0.1 mmol of **1**; 1.0 mmol of acyl donor; 500 U enzyme; 5 ml acetone; water activity (aw) = 0.07; 45 °C; 150 rpm
[b]The reaction condition: 5 mg of lipase; 0.1 mmol of **1**; 1.0 mmol of acyl donor; 3 mL of acetone and incubated at 55 °C; 100 rpm for 5 h
[c]nd: not determined.

Amano lipase AK (*P.fluorescens*) are temperature in the range from 50 to 55 °C with an incubation period of 5 hrs in acetone.

3. Whole- cell transformation

Fungal cultures are capable of catalyzing different chemical transformations such as hydroxylation, reduction, elimination, oxidation, rearrangement *etc*. The fungus catalyzed biotransformations of principal diterpenoids extracted from *Andrographis paniculata* is studied by several research groups to assess the structure-activity relationship and to find new chemical entities with better medicinal properties. Different fungal cultures were screened for the hydroxylation, reduction as well as oxidation of andrographolide (**1**) and other isolated labdane diterpenes (**2**–**4**), Table 3. Few transformations were lead to the novel compounds and further investigation of their biological activities revealed the improvement in the efficacy as compared to the parent compounds.

Andrographolide (**1**) was biotransformed by *Rhizopus stolonifer* ATCC 12939 into ten oxygenated and dehydrated bioconversion products (He et al. 2010). The bioconversion was carried out by shake flask fermentation in potato medium at 28 °C for 96 hrs. The extracted metabolites were characterized by spectroscopic techniques and indentified as 12(*R*),13(*R*)-12-hydroxyandrographolide (**6**), 12(*S*),13(*S*)-12-hydroxyandrographolide (**7**), isoandrographolide (**9**), 3-dehydro-isoandrographolide (**10**), 14-deoxy-11,12-didehydroandrographolide (**3**), 3-oxo-14-deoxy-11,12-didehydroandrographolide (**11**), 3-dehydroandrographolide (**8**), 14-deoxyandrographolide (**4**), 3-dehydro-14-deoxyandrographolide (**12**) and 3-dehydro-14-deoxyandrographolide-19-oic acid (**13**). Among the identified compounds **10** and **13** were novel metabolites. Further, the structure-activity relationship of the metabolites was studied by testing their antiproliferative activities against human breast cancer (MCF-7), human colon cancer (HCT-116) and human leukaemia (HL-60) cell lines. Results of the experiments showed a considerable and slight decrease in the antiproliferative activity of **1** on oxidation of α-hydroxy group at C-3 carbon to keto group and hydration of $\Delta^{12,13}$ double bond respectively, whereas no effect on activity was observed after dehydration of hydroxyl group at C-14 (Scheme 2).

Biocatalytic transformation of andrographolide (**1**) using *Aspergillus ochraceus* (ATCC 1008) afforded five regioselective hydroxylated, dehydrated and oxidized products (He et al. 2011). During transformation, **1** was incubated with fungal culture in fermentation media for 96 hrs at a concentration of 4.8 mg/mL. The metabolites were isolated from the fermentation media and characterized as 14-deoxy-11,12-didehydroandrographolide (**3**), 14-deoxy-11,12-didehydroandrographolide 19-oic acid (**14**), 8β-hydroxy-8(17)-dihydro-14-deoxy-11,12-didehydroandrographolide (**15**), 8β-hydroxy-8(17)-dihydro-14-deoxy-11,12-didehydroandrographolide 19-oic acid (**16**) and 8β-hydroxy-8(17)-dihydroandrographolide (**17**). Out of the isolated metabolites **15**, **16** and **17** were novel compounds. Isolated metabolites were investigated for cytotoxic activity by MTT assay. Most of the bioconversion products showed considerable cytotoxic activity against human colon cancer (HCT-116), human breast cancer (MCF-7) and leukaemia (HL-60) cell lines (Scheme 3). Further, andrographolide (**1**) was isomerized and dehydrated to form 14-deoxy-11,12-didehydroandrographolide (**3**) and andropanolide (**18**) in a regio- and stereoselective manner (Sultan et al. 2014) using two fungal cultures *viz. Cunninghamella elegans* (TSY 0865) and *Cephalosporium aphidicola* (IMI-68689) (Scheme 4).

FengQiu *et al.* has investigated the microbial transformation of neoandrographolide (**2**), one of the major constituent of ene-labdane diterpenods obtained from *Andrographis paniculata* using *Aspergillus niger* (AS 3.739) (Chen et al. 2007). After whole-cell transformation of **2**, five metabolites viz. 8(17),13-ent-labdadien-16,15-olid-19-oic acid (**19**), 19-hydroxy-8(17),13-ent-labdadien-16,15-olide (**20**), 18-hydroxy-8(17),13-ent-

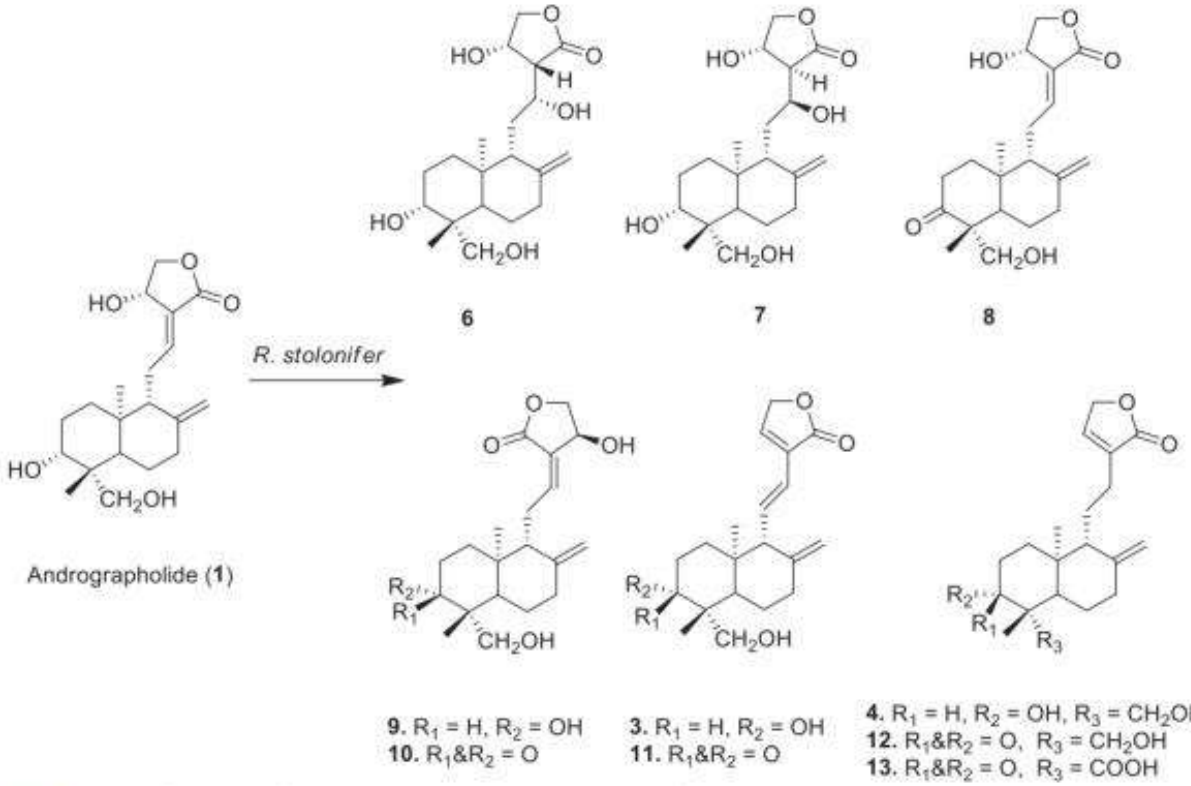
Table 3. Whole-cell transformations of labdane diterpenoid from *A. paniculata*.

Sr. No.	Labdane diterpenoid (substrate)	Fungal culture (biocatalyst)	Transformation products
1	Andrographolide (**1**)	*Rhizopus stolonifer* (ATCC 12939) (He et al. 2010)	12(*R*),13(*R*)-12-hydroxyandrographolide (**2**), 14-deoxy-11,12-didehydroandrographolide (**3**), 14-deoxyandrographolide (**4**), 12(*S*),13(*S*)-12-hydroxyandrographolide (**7**), 3-dehydroandrographolide (**8**), isoandrographolide (**9**), 3-dehydro-isoandrographolide (**10**), 3-oxo-14-deoxy-11,12-didehydroandrographolide (**11**), 3-dehydro-14-deoxyandrographolide (**12**), 3-dehydro-14-deoxyandrographolide-19-oic acid (**13**).
2	Andrographolide (**1**)	*Aspergillus ochraceus* (ATCC 1008) (He et al. 2011)	14-deoxy-11,12-didehydroandrographolide 19-oic acid (**14**), 8β-hydroxy-8(17)-dihydro-14-deoxy-11,12-didehydroandrographolide (**15**), 8β-hydroxy-8(17)-dihydro-14-deoxy-11,12-didehydroandrographolide 19-oic acid (**16**), 8β-hydroxy-8(17)-dihydroandrographolide (**17**), 14-deoxy-11,12-didehydroandrographolide (**19**).
3	Andrographolide (**1**)	*Cunninghamella elegans* (TSY 0865) (Sultan et al. 2014)	14-deoxy-11,12-didehydroandrographolide (**3**)
4	Andrographolide (**1**)	*Cephalosporium aphidicola (IMI-68689)* (Sultan et al. 2014)	andropanolide (**18**)
5	Neoandrographolide (**2**)	*Aspergillus niger* (AS 3.739) (Chen et al. 2007)	3α-hydroxy-8(17),13-ent-labdadien-16,15-olid-19-oic acid (**4**), 8(17),13-ent-labdadien-16,15-olid-19-oic acid (**19**), 19-hydroxy-8(17),13-ent-labdadien-16,15-olide (**20**), 18-hydroxy-8(17),13-ent-labdadien-16,15-olid-19-oic acid (**21**), 8β,19-dihydroxy-ent-labd-13-en-16,15-olide (**22**)
6	Neoandrographolide (**2**)	*Mucor spinosus* (AS 3.2450) (Wang et al. 2011)	14-deoxyandrographolide (**4**), 8(17),13-ent-labdadien-16,15-olid-19-oic acid (**19**), 3,14-dideoxyandrographolide (**20**), phlogantholide-A (**23**), 7β-hydroxy-3,14-dideoxyandrographolide (**24**), 19-[(β-D-glucopyranosyl)oxy]-19-oxo-ent-labda-8(17),13-dien-16,15-olide (**25**), 8β,17,19-trihydroxy-ent-labd-13-en-16, 15-olide (**26**), 17,19-dihydroxy-7,13-ent-labdadien-16,15-olide (**27**), 17,19-dihydroxy-8,13-entlabdadien- 16,15-olide (**28**), 8β,17β-epoxy-3,14-dideoxyandrographolide (**29**).
7	Dehydroandrographolide (**3**)	*Cunninghamella elegans* (Xinac et al. 2009)	3-oxo-dehydroandrographolide (**30**), 3-oxo-2β-hydroxy-dehydroandrographolide (**31**), 3-oxo-8β,17α-epoxydehydroandrographolide(**32**), 3,19-dihydroxy-7,11,13-ent-labdatrien-15,16-olide (**33**)
8	Dehydroandrographolide (**3**)	*Cunninghamella echinulata* (AS 3.3400) (Xin et al. 2009)	3-oxo-hydroxydehydroandrographolide (**30**), 7α-hydroxydehydroandrographolide (**34**), 9β-hydroxydehydroandrographolide (**35**), 8β,17α-epoxydehydroandrographolide (**36**), 3-oxo-9β-hydroxydehydroandrographolide (**37**),
9	Dehydroandrographolide (**3**)	*Cunninghamella blakesleana* (AS 3.970) (Chena et al. 2011)	3-oxo-dehydroandrographolide (**20**), 8β,17α-epoxydehydroandrographolide (**24**), 3-oxo-8β,17α-epoxydehydroandrographolide (**27**), 9β-hydroxydehydroandrographolide (**35**), 3-oxo-9β-hydroxydehydroandrographolide (**37**) 3α, 12S, 19-trihydroxy-8(17), 9(11)-*ent*-labdadien-16, 15-olide (**38**) 14-deoxy-12*R*-hydroxyandrographolide (**39**)
10	Deoxyandrographolide (**4**)	*Cunninghamella blakesleana* (AS 3.970) (Chena et al. 2011)	3-oxo-14-deoxyandrographolide (**12**), 3α,17,19-trihydroxy-7,13-*ent*-labdadien-16,15-olide (**40**), 7*S*-hydroxy-14- deoxyandrographolide (**42**), 3-oxo-7*R*-hydroxy-14-deoxyandrographolide (**43**), 8β,17α- epoxy-14-deoxyandrographolide (**44**) 3-oxo-8β,17α-epoxy-14-deoxyandrographolide (**45**) 3α,17,19-trihydroxy-8,13-*ent*-labdadien-16, 15-olide (**41**), 3-oxo-8α,17β-epoxy-14-deoxyandrographolide (**46**) 9β-hydroxy-14-deoxyandrographolide (**47**)
11	Deoxyandrographolide (**4**)	*Fusarium graminearum* (AS 3.4598) (Xin et al. 2011)	3-oxo-14-deoxyandrographolide (**12**), 7β-hydroxyl-14-deoxyandrographolide (**42**), 3-oxo-8α,17β-epoxy-14-deoxyandrographolide(**46**), 1β-hydroxyl-14-deoxyandrographolide (**48**), 3-oxo-17,19-dihydroxyl-8,13-*ent*-labdadien-15,16-olide (**49**)

(*continued*)

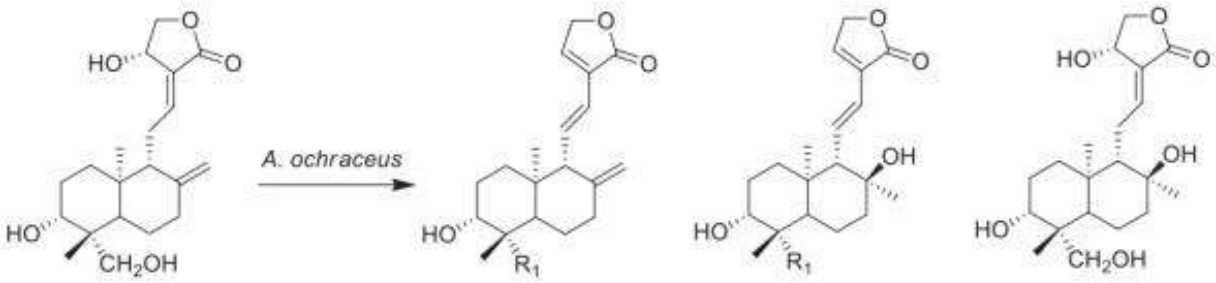
Table 3. Continued.

Sr. No.	Labdane diterpenoid (substrate)	Fungal culture (biocatalyst)	Transformation products
12	Deoxyandrographolide (**4**)	*Alternaria alternate* (AS 3.4578) (Xin et al. 2011)	dehydroandrographolide (**3**), 9β-hydroxydehydroandrographolide (**35**), 3α,17,19-trihydroxyl-8,13-*ent*-labdadien-15,16-olide (**41**), 9β-hydroxydeoxyandrographolide (**47**), 3-oxo-9β-hydroxydeoxyandrographolide (**50**)
13	Deoxyandrographolide (**4**)	*Cunninghamella blakesleana* (AS 3.2004) (Xiao et al. 2012)	3-oxo-17,19-dihydroxy-7,13-*ent*-labdadien-15,16-olide (**40**), 3-oxo-2β-hydroxy-14-deoxyandrographolide (**55**), 3-oxo-1β-hydroxy-14-deoxy-andrographolide (**56**), 3-oxo-19-hydroxy-1,13-*ent*-labdadien-15,16-olide (**57**) Other 21 metabolites (Scheme 13)
14	Deoxyandrographolide (**4**)	*Cunninghamella echinulata* (AS 3.3400) (Li et al. 2011)	3α,17,19-trihydroxyl-7,13-ent-labdadien-15,16-olide (**41**), 3-oxo-7α-hydroxy-14-deoxyandrographolide (**43**), 3-oxo-8β,17α-epoxy-14-deoxyandrographolide (**45**), 8α-formyl-14-deoxyandrographolide (**59**) 8β-methoxyl-17α-hydroxyl-14-deoxyandro-grapholide (**60**) 7β-hydroxy-14-deoxyandrographolide (**42**), 3-oxo-14-deoxyandrographolide (**12**), dehydroandrographolide (**3**), 8β, 17α-epoxy-dehydroandrographolide (**44**), 9β-hydroxy-dehydroandrographolide (**35**), 3-oxo-9β-hydroxydehydroandrographolide (**37**)

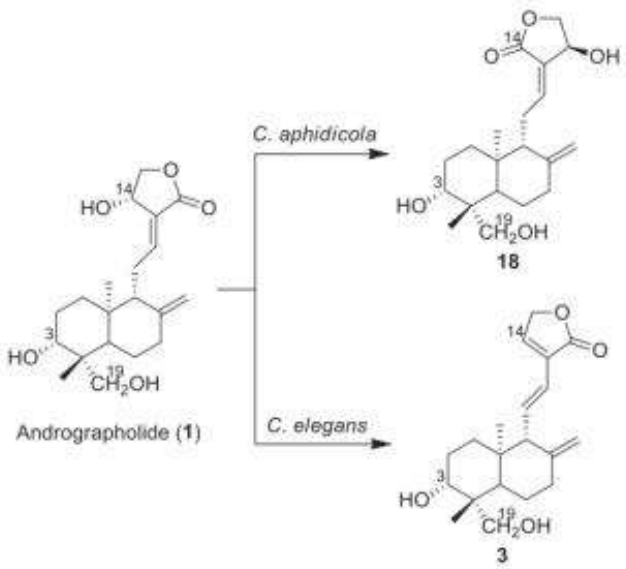


Scheme 2. Biotransfromation of androghapholide (**1**) by *Rhizopus stolonifer*.

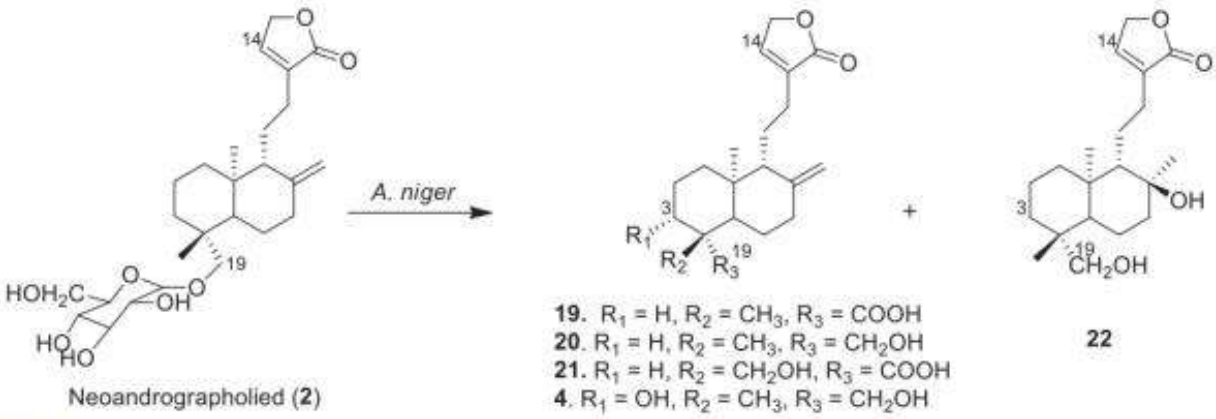
labdadien-16,15-olid-19-oic acid (**21**), 3α-hydroxy-8(17), 13-ent-labdadien-16,15-olid-19-oic acid (**4**) and 8β,19-dihydroxy-ent-labd-13-en-16,15-olide (**22**) were isolated and purified from fermentation media. Out of the isolated metabolites, **21** and **22** were new compounds. The preparative scale biotransformation of **2** (2 gm) was carried out in 150 mL fermentation media and the transformed products were identified by spectroscopic techniques. (Scheme 5). The fungal culture *Mucor spinosus* (AS 3.2450) have transformed



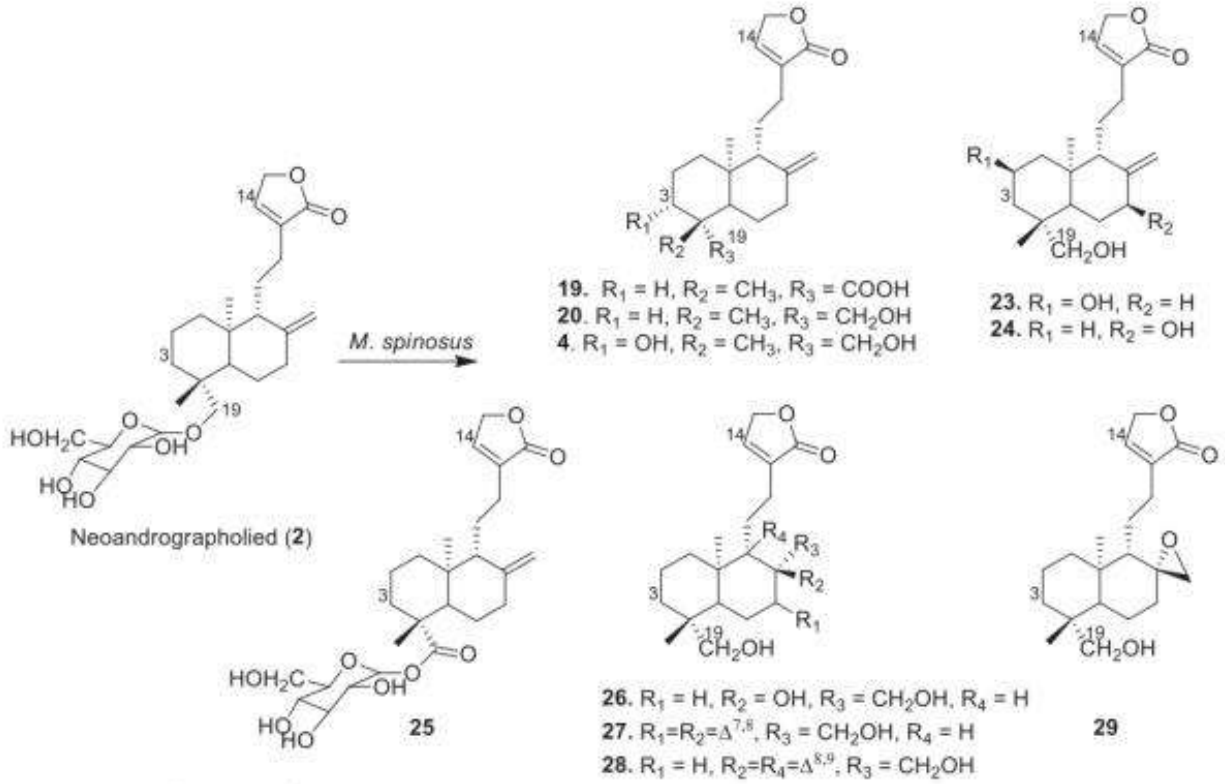
Scheme 3. Biotransfromation of androghapholide (1) by *Aspergillus ochraceus*.



Scheme 4. Biotransformation of andrographolide (1) by *Cunninghamella elegans* and *Cephalosporium aphidicola*.



Scheme 5. Biotransformation of neoandrographolied (2) by *Aspergillus niger*.

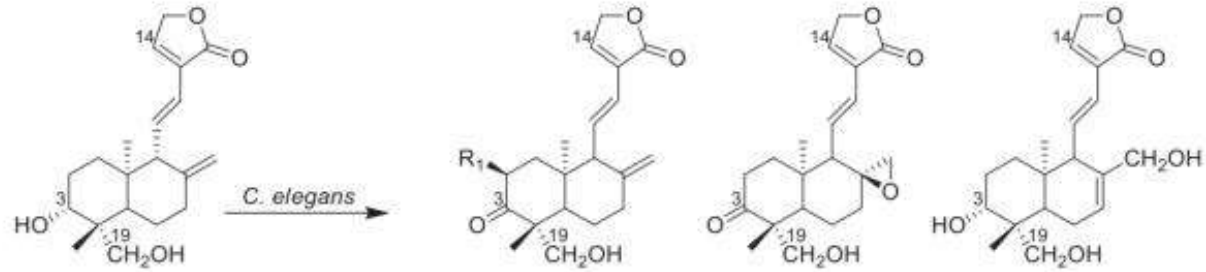


Scheme 6. Biotransformation of neoandrographolied (2) by *Mucor spinosus*.

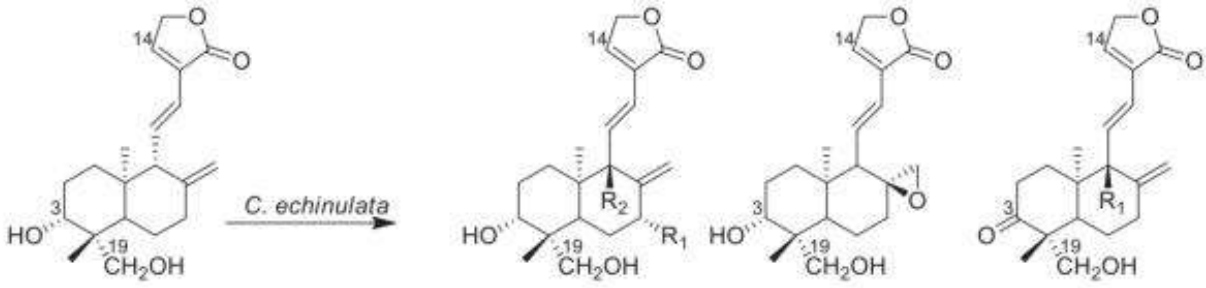
neoandrographolide (**2**) in fermentation media into different metabolites (Wang et al. 2011). Different kind of enzymatic reactions such as hydroxylation, oxidation, glycosylation, epoxidation and elimination had occurred after 3 days incubation of **2** with *M. spinosus*. Total ten biotransformed products were isolated from fermentation media *viz*., 14-deoxyandrographolide (**4**), 8(17),13-ent-labdadien-16,15-olid-19-oic acid (**19**), 3,14-dideoxyandrographolide (**20**), phlogantholide-A (**23**), 7β-hydroxy-3,14-dideoxyandrographolide (**24**), 19-[(β-D-glucopyranosyl)oxy]-19-oxo-ent-labda-8(17),13-dien-16,15-olide (**25**), 8β,17,19-trihydroxy-ent-labd-13-en-16, 15-olide (**26**), 17,19-dihydroxy-7,13-ent-labdadien-16,15-olide (**27**), 17,19-dihydroxy-8,13-entlabdadien- 16,15-olide (**28**) and 8β,17β-epoxy-3,14-dideoxyandrographolide (**29**). Among the transformed products five viz. **24**, **25**, **27**,**28,** and **29** were new compounds. The effect of isolated metabolites on nitric oxide production induced by LPS in macrophages was investigated. Some metabolites showed inhibitory effect on NO production same as **2** (Scheme 6).

Dehydroandrographolide also known as 14-deoxy-11,12-didehydroandrographolide (**3**) is an active phytochemical extracted from *A. paniculata*. It is transformed into its derivatives by different *Cunninghamella sp*. The transformation of 14-deoxy-11,12-didehydroandrographolide (**3**) using *Cunninghamella elegans* resulted into four metabolites *viz*., 3-oxo-dehydroandrographolide (**30**), 3-oxo-2β-hydroxy-dehydroandrographolide (**31**), 3-oxo-8β,17α-epoxydehydroandro grapholide (**32**), 3,19-dihydroxy-7,11,13-ent-labdatrien-15,16-olide (**33**) out of which **31** to **33** metabolites were new compounds (Xin et al. 2009). During transformation 500 mg of **3** was incubated with fungal culture for 6 days in the fermentation media (Scheme 7). Highly regio-specific hydroxylation of dehydroandrographolide (**3**) at C-9 was observed on incubation with *Cunninghamella echinulata* AS 3.3400 in 72% yield. Five metabolites were isolated from fermentation media and identified as 3-oxo-hydroxydehydroandrographolide (**30**), 7α-hydroxydehydroandrographolide (**34**), 9β-hydroxydehydroandrographolide (**35**), 8β,17α-epoxydehydroandro-grapholide (**36**) and 3-oxo-9β-hydroxydehydroandrographolide (**37**), respectively. Out of the purified metabolites three were novel compounds (**34**, **35** and **37**). The cytotoxicity study indicated that metabolite **35** has more activity as compared to the substrate **3** (Xin, Su, et al. 2009) (Scheme 8).

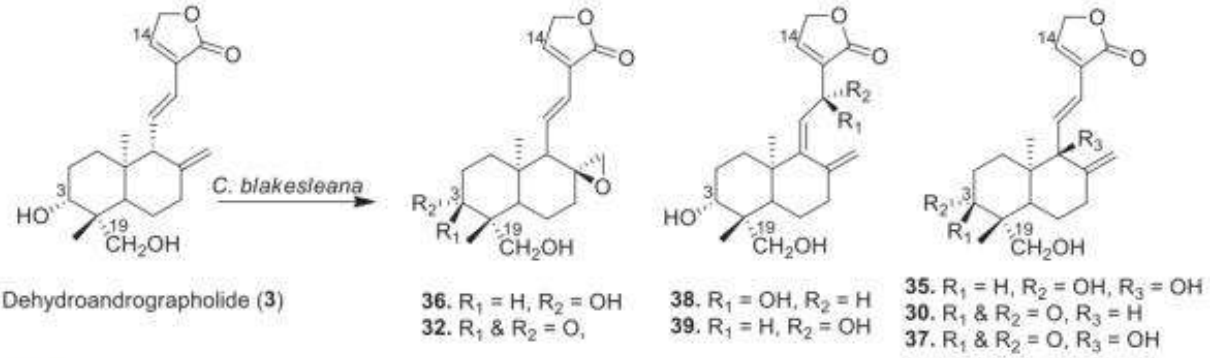
The fungal culture *Cunninghamella blakesleana* (AS 3.970) has efficiently transformed dehydroandrographolide (**3**) into seven oxidised derivatives (Chena



Scheme 7. Biotrasformation of 14-deoxy-11,12-didehydroandrographolide (3) by Cunninghamella.



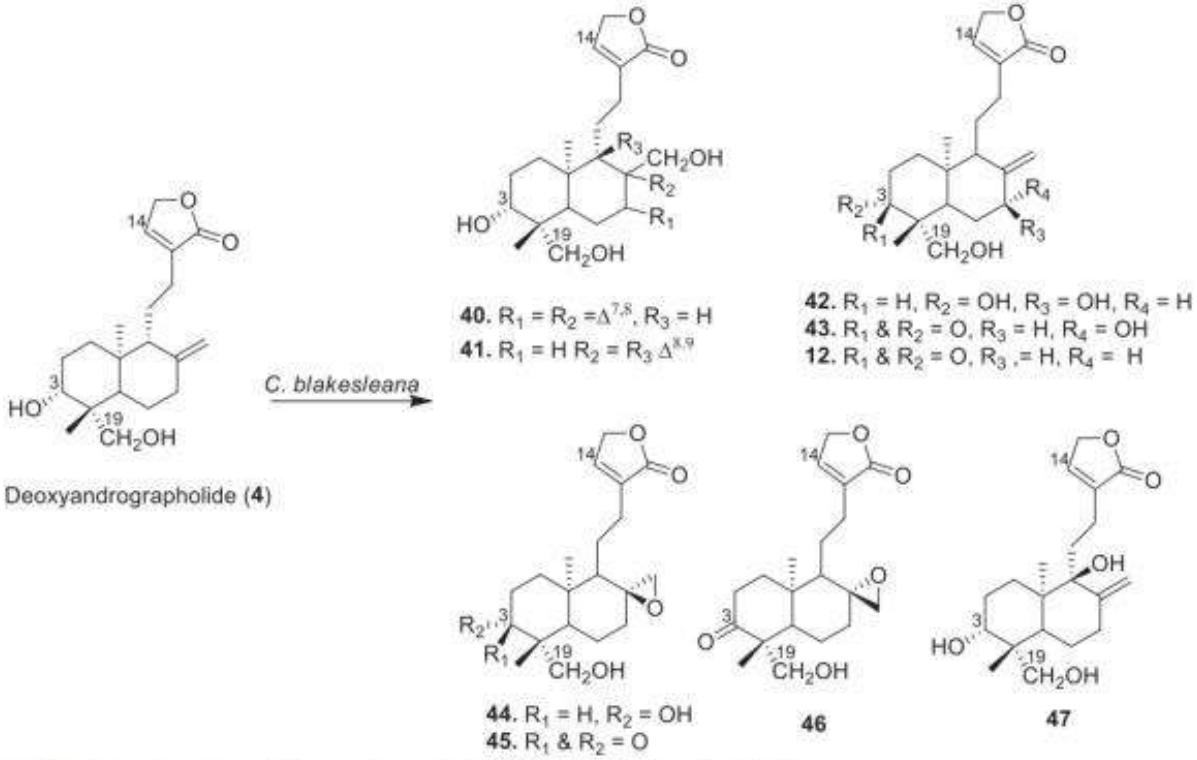
Scheme 8. Biotrasformation of dehydroandrographolide (3) by *Cunninghamella echinulata*.



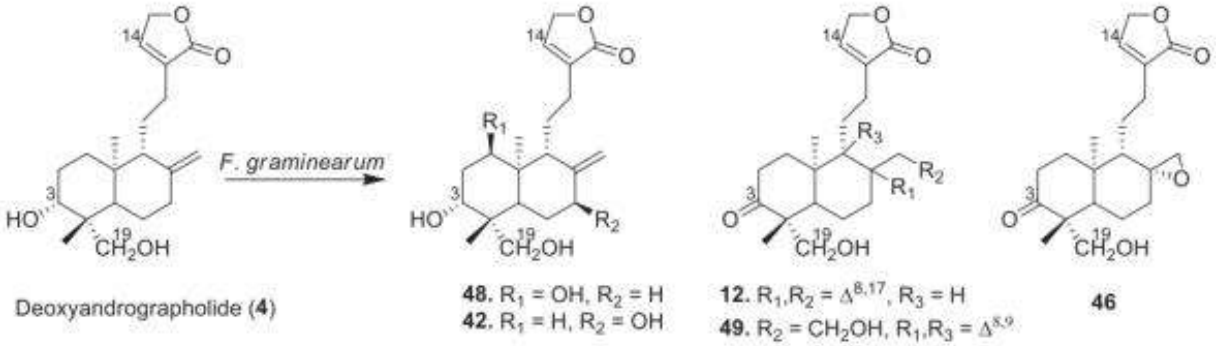
Scheme 9. Biotrasformation of dehydroandrographolide (3) by *Cunninghamella blakesleana*.

et al. 2011). The transformation afforded 3α, 12S, 19-trihydroxy-8(17), 9(11)-*ent*-labdadien-16, 15-olide (**38**) new compound. Other six metabolites were characterized by comparing their spectroscopic data with reports in the literature and identified as 3-oxo-dehydroandrographolide (**30**), 8β,17α-epoxydehydroandrographolide (**36**), 3-oxo-8β,17α-epoxydehydro andrographolide (**32**), 9β-hydroxydehydroandrographolide (**35**), 3-oxo-9β-hydroxydehydroandrographolide (**37**) and 14-deoxy-12*R*-hydroxyandrographolide (**39**). The evaluation of inhibitory activity of the isolated metabolites on nitric acid production in lipopolysaccharide-activated macrophages provided preliminary information about the structure-activity relationship (SAR) which can be extended to establish **3** as anti-inflammatory agents (Scheme 9).

The diterpene lactone, deoxyandrographolide (**4**) obtained from *A. paniculata* exhibits anti-cancer and anti-inflammatory activity (Dai et al. 2019). It is also known as 14-deoxy-didehydroandrographolide (**4**). The microbial transformations of **4** have been carried out for finding the derivatives with better bioactivity and



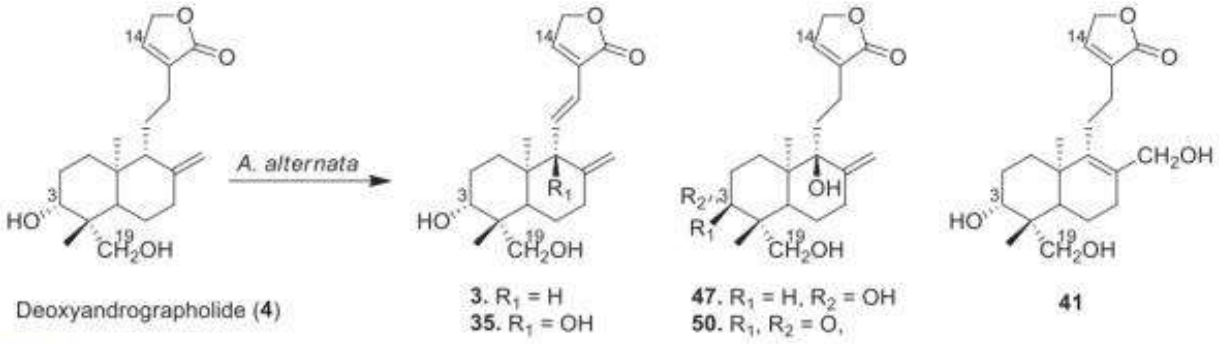
Scheme 10. Biotrasformation of deoxyandrographolide (4) by *Cunninghamella blakesleana*.



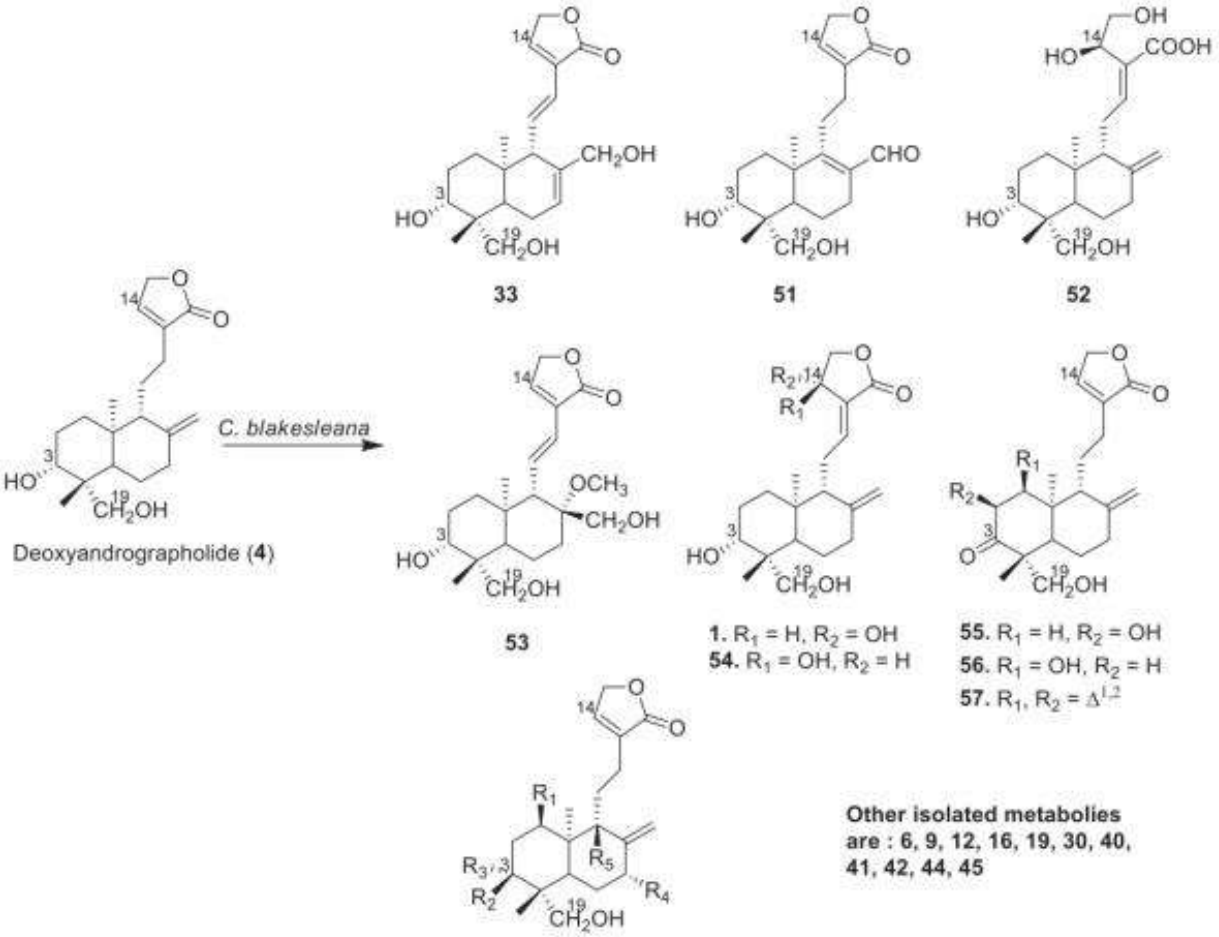
Scheme 11. Biotransformation of deoxyandrographolide (4) by *Fusarium graminearum*.

water-solubility properties. The fungal transformation of deoxyandrographolide (**4**) by *Cunninghamella blakesleana* (AS 3.970) in the potato medium with substrate concentration of 4 mg/mL at 28 °C for 48 hrs yielded three novel metabolites *viz.*, 3α,17,19-trihydroxy-8,13-*ent*-labdadien-16, 15-olide (**41**), 3-oxo-8α,17β-epoxy-14-deoxyandrographolide (**46**) and 9β-hydroxy-14-deoxyandrographolide (**47**) (Chena et al. 2011). Other known six metabolites isolated from fermentation media are 3-oxo-14-deoxyandrographolide (**12**), 3α,17,19-trihydroxy-7,13-*ent*-labdadien-16,15-olide (**40**), 7*S*-hydroxy-14- deoxyandrographolide (**42**), 3-oxo-7*R*-hydroxy-14-deoxyandrographolide (**43**), 8β,17α- epoxy-14-deoxyandrographolide (**44**) and 3-oxo-8β,17α-epoxy-14-deoxyandrographolide (**45**). All the isolated metabolites were evaluated for nitric acid production inhibition activity in lipopolysaccharide-activated macrophages to reveal structure-activity relationship (SAR) (Scheme 10).

The regioselective transformation of deoxyandrographolide (**4**) by *Fusarium graminearum* (AS 3.4598) for 5 days, leads to different enzymatic reactions such as hydroxylation, epoxidation and oxidation (Xin, Cui, et al. 2011). The transformation afforded five more polar products, 3-oxo-14-deoxyandrographolide (**12**), 7β-hydroxyl-14-deoxyandrographolide (**42**), 3-oxo-8α,17β-



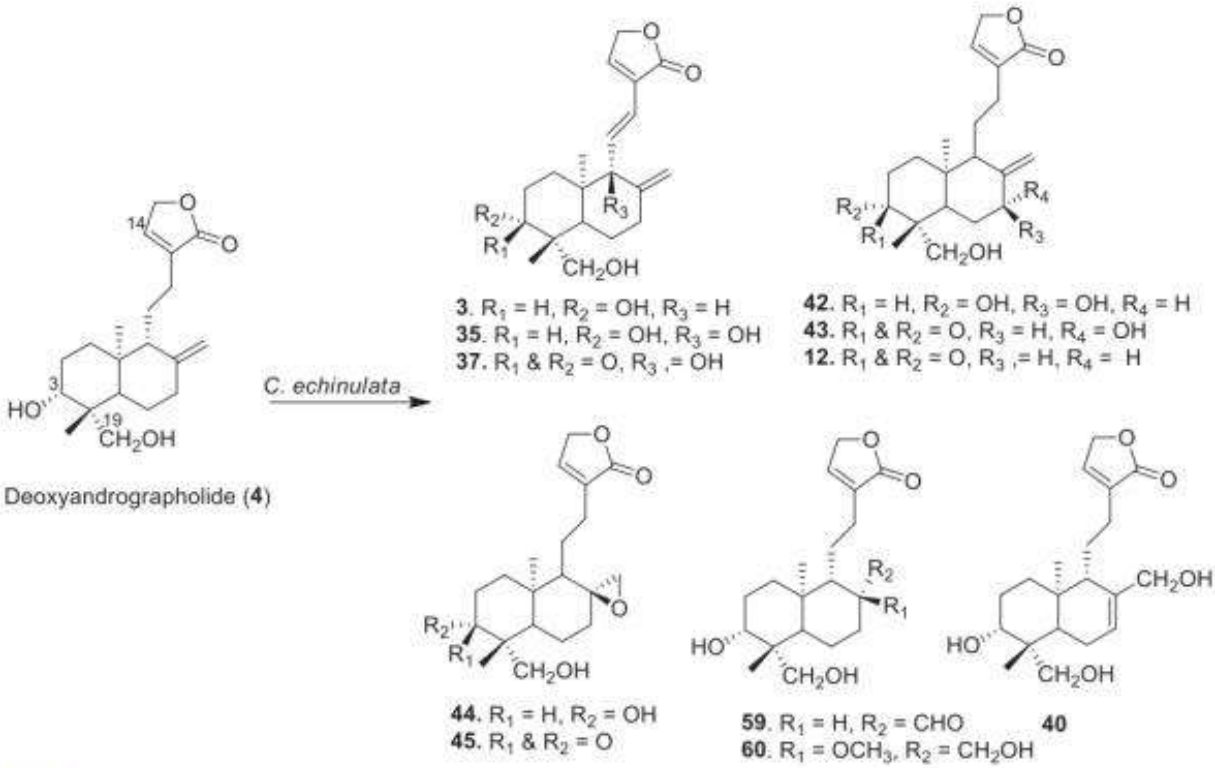
Scheme 12. Biotransformation of deoxyandrographolide (4) by *Alternaria altern.*



Scheme 13. Biotransformation of deoxyandrographolide (4) by *Cunninghamella blakesleana.*

epoxy-14-deoxyandrographolide (**46**), 1β-hydroxyl-14-deoxyandrographolide (**48**) and 3-oxo-17,19-dihydroxyl-8,13-*ent*-labdadien-15,16-olide (**49**), out of which compounds **46**, **48** and **49** were novel (Scheme 11).

The fungal culture *Alternaria alternate* (AS 3.4578) have hydroxylated deoxyandrographolide (**4**) after fermentation into dehydroandrographolide (**3**), 9β-hydroxydehydroandrographolide (**35**), 3α,17,19-trihydroxyl-8,13-*ent*-labdadien-15,16-olide (**41**), 9β-



Scheme 14. Biotrasformation of deoxyandrographolide (4) by *Cunninghamella echinulata*.

hydroxydeoxyandrographolide (**47**), and 3-oxo-9β-hydroxydeoxyandrographolide (**50**) (Xin et al. 2011) (Scheme 12). In continuance, Deng et al. (2012) have investigated the transformation of deoxyandrographolide (**4**) by *Cunninghamella blakesleana* (AS 3.2004). On 5 days incubation with *C. blakesleana*, the substrate **4** was transformed into twenty five different analogues, among them four metabolites *viz*.,3-oxo-17,19-dihydroxy-7,13-*ent*-labdadien-15,16-olide (**40**), 3-oxo-2β-hydroxy-14-deoxyandrographolide (**55**), 3-oxo-1β-hydroxy-14-deoxy-andrographolide (**56**) and 3-oxo-19-hydroxy-1,13-*ent*-labdadien-15,16-olide (**57**) were new compounds. All isolated metabolites were analyzed for the cytotoxic activities on RAW 264.7 macrophages and inhibitory activities against LPS-induced NO production in RAW 264.7 macrophages. The SAR studies indicated that γ-butyrolactone and epoxy moieties may be responsible for cytotoxic activity. Further, it was evaluated that presence of the 3-ketone group, γ-butyrolactone or the absence of hydroxyl group at C-3 are the key functional groups responsible for enhancing the inhibitory activity of **5** (Scheme 13).

The fungus *Cunninghamella echinulata* (AS 3.3400) have metabolized deoxyandrographolide (**4**) to eleven derivatives (Li et al. 2011). Out of the purified metabolites five were novel compounds and characterized as 3α,17,19-trihydroxyl-7,13-ent-labdadien-15,16-olide (**40**), 3-oxo-7α-hydroxy-14-deoxyandrographolide (**43**), 3-oxo-8β,17α-epoxy-14-deoxyandrographolide (**45**), 8α-formyl-14-deoxyandrographolide (**59**) and 8β-methoxyl-17_-hydroxyl-14-deoxyandro-grapholide (**60**). The *in vitro* cytotoxicities of metabolites were determined against MCF and A562 cells by the MTT bioassay. The SAR study revealed that presence of the carbonyl group at C-3 improves cytotoxic activity whereas there is no significant effect on activity due to hydroxylation at C-17 (Scheme 14).

4. Conclusion

In summary, whole-cell and pure enzyme catalysed transformations is an attractive, cost effective and environment friendly alternative tool for the regioselective derivatization of bioactive labdane diterpenes isolated from *Andrographis paniculata*. The transformation processes can further be standardised and scaled up to commercial scale for industrial production. Consequently, exploring a wide range of biocatalysts as well as integrating the biotransformation process with chemical synthesis are promising approaches to prepare wide range of diterpene derivatives, which

can be probed as novel lead molecules in pharmaceutical and medicinal field.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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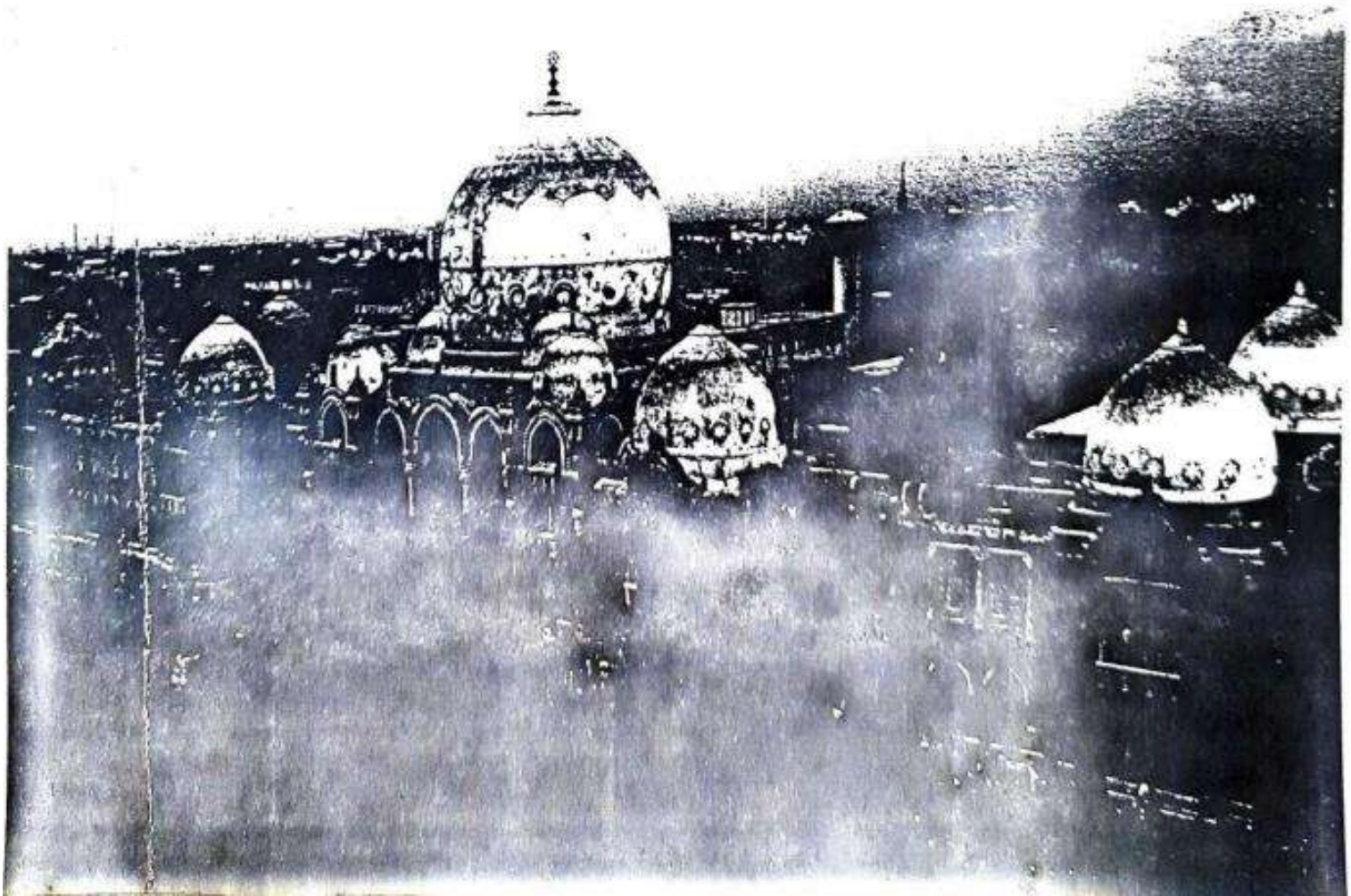

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THERMO STUDY OF COMMERCIAL SAMPLES OF *LOHABHASMA*

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Abstract:
Ayurved firstly introduced the concept of *'bhasma'* in its medicinal system but, it is difficult to trace out the origin of this concept, although references regarding the term *'bhasma'* are found in ancient *sanskrit* literature. From the citations related to *'bhasma'* in original *sanskrit* texts, it seems that *bhasma* obtained from calcination of (i) living as well as non-living matters (ii) vegetable as well as non-vegetable materials, possessed some special significance and importance in various religions functions, yoga and meditations.

In this research article I have done the comparative study of thermogravimetric analysis of two commercial samples of lohabhasma. Traditional method of preparation of lohabhasma is also important. Originally, *ayurvedic* system of medicine was mostly restricted to medicinal plants (*vanaushdi*) and to some extent to animal products such as cow-urine, cow-dung, cow-milk, honey etc. Later on metal-based *bhasmas* were introduced and subsequently they constituted the most important class of drugs of mineral origin. *ayurved* and *ayurvedic* medicines will receive more and more appreciation and importance all over the world. Metal-based *ayurvedic* drugs being the superior drugs as compared to all other classes of drugs, there is an excellent opportunity to rejuvenate this original art with the help of modern scientific development.
Keywords: *lohabhasma, ayurved, vanaushdi, drugs, cowurine*

Introduction:

Iron, being an element of vital importance, in life process, possesses equal importance in all medical systems, eastern or western. Therefore, iron based medicinal preparations are pharmaceutical products of common interest of all pharmacies. *Lohabhasma* is one of such product for which there is large scale demand both for clinical purpose as well as for other *ayurvedic* formulations of which *lolabhasma* is an important constituent. Accordingly, the number of *ayurvedic* pharmacies and modern pharmacies, preparing *lohabhasma* on small or large scale is tremendous and, in every state, *lohabhasma* is prepared by traditional methods. The selection of particular method depends on the location of the pharmacy and availability of the raw materials required for synthesis.

All the commercial samples sold in the market in India may be broadly divided into two or three categories as Ordinary *lohabhasma* prepared from metallic iron, which is synthesized by some traditional process, the details of which are not specified. Since cheaper or waste iron powder or sheets are used as starting materials and readily available media are used such as cow-urine or medicinal plant materials are used for *bhasmikarana*, these are much cheaper and therefore they are commonly used for clinical purpose. *Anta lohabhasma* prepared by using magnetite or other type of magnetic iron as the starting material. This is more costly and prepared by some *ayurvedic* physicians for their treatment. Here also the method of synthesis is neither specified nor literature reference is given.

From medicinal point of view, no significant difference in the properties of *lohabhasma* belonging to any category is reported along with experimental supports. Therefore, all the commercial samples are more or less similar in their quality and utility. Due to this reason, and because the number of pharmacies is very large, only representative pharmacies from different states are listed in Table 1 For *lohabhasma* some work has been carried out by us previously.

But the present work is the first attempt to carry out a systematic work on comparative study of two commercial samples using modern techniques such as **thermogravimetric analysis**. Comparative study of the commercial samples of metal-based *ayurvedic bhasmas* is one of our main activity during past few years.

Experimental Procedure.

In this method firstly the iron powder (500g) was subjected to general method of purification in which the powder was heated to red heat and then dipped successively in *til* oil, butter milk, cow urine and aqueous extract of dolichos (*kulith*) and rice (*kanji*). For special purification, the above processed iron powder (500g) was heated and dipped in freshly collected cow-urine. This operation of heating and dipping the hot iron powder in cow urine was repeated seven times.

After special purification, the iron powder was taken in a mortar and mixed with cow-urine and the mixture was triturated for six hours. This mixture was kept overnight for interaction to complete the destruction of metallic state (*marana*).

SOME REPRESENTATIVE *AYURVEDIC* PHARMACIES MANUFACTURING *LOHABHASMA*

Table 01 Representative *ayurvedic* pharmacies, which manufacture *lohabhasma*

No.	Name of the pharmacy	Place	State
1	Kalpataru Ayurvedic works Ltd.	Kolkatta	West Bengal
2	Dhanwantari	Mumbai	Maharastra
3	Deendayal Ayurved Pharmacy		Madya Pradesh
4	Unza Pharmacy	Unza	Gujrat

5	Dabur pharmaceutical works	Sahibabad	Uttarpradesh
6	Krishna Gopal Ayurved Bhavan	Ajmer	Rajasthan
7	Dootpapeshwar	Panvel	Maharastra
8	Ayurved Seva Sangh	Pune	Maharastra

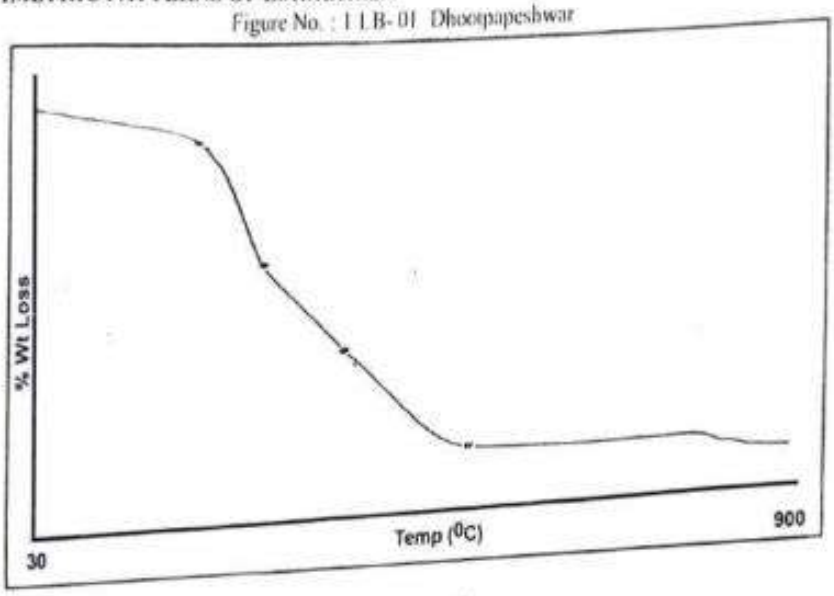
In the present work about two such pharmacies are selected and their names and places are given in Table 02 . Selection of ayurvedic pharmacies for comparative study.

Table-02

Sr No	Code Name and Name of Pharmacy	Name and Place of Pharmacy
1	LB-01 Dootpapeshwar	Dootpapeshwar Panvel
3	LB-02 Ayurved Seva Sangh	Ayurved Seva Sangh Pune

THERMOGRAVIMETRIC PATTERNS OF *LOHABHASm*

Figure No. : 1 LB- 01 Dhootpapeshwar



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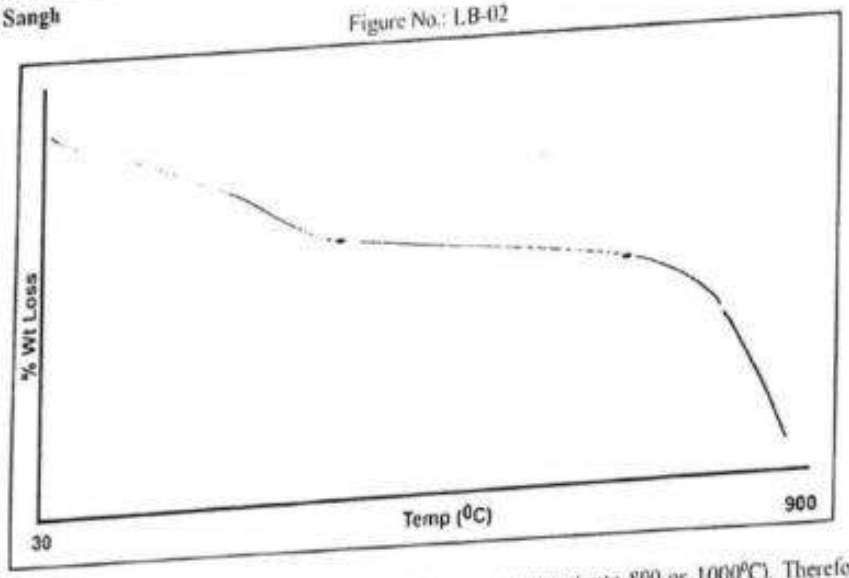
Ayurved Seva Sangh

Figure No.: LB-02



Result

Most of the metallic *bhasmas* are synthesized by applying higher temperatures (upto 800 or 1000°C). Therefore, they are not expected to show any significant thermal decomposition behavior in the temperature range (25-600)°C, if they are purely metal oxides as assumed by some modern scientists. But still their thermogravimetric study may be found to be useful in certain aspects such as

a. Presence or absence of adhered, or absorbed water or moisture.

indications of any decomposable organic matter associated with these *bhasmas*, if any and similarities or differences in thermal decomposition behavior among different commercial samples which might be reflected in their TG curves.

Therefore, study of some commercial samples LB-01, and LB-02 was carried out to examine their thermal decomposition behavior. For this purpose, the thermograms of these samples of *lohabhasma* were recorded in air atmosphere on a NATZSCH simultaneous thermo analyzer STA.40 a model provided with platinum thermo cups and Pt/Pt/ 10% Rh thermocouples. For each run about 20-25 mg of a well ground sample was taken and the heating rate was maintained at 10°C per minute. The nature of the TG curves is shown in Figure 1 to 2 On the basis of T.G. patterns samples of *Lohabhasma* may be classified into two groups. One group consisting of Fe-BAI and Fe-R.This shows thermal stability of the samples over the entire range R.T. to 900°C. This shows different behavior. These samples show two to three stage decomposition patterns indicating that they consists decomposable organic matter. From this it may be concluded that the methods of preparation of *Lohabhasma* are different from one another, due to which end products are not identical.

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Sodium Alginate Biopolymer: An Efficient, Recyclable Green Catalyst for the Synthesis of Chalcone Derivatives under Mild Conditions

Manisha A. Bora

One-pot chemical synthesis of highly pure chalcone under mild conditions using biocompatible Na-alginate biopolymer is reported. Several chalcone derivatives are prepared by magnetic stirring the equimolar quantities of the appropriate methyl ketone and aryl aldehyde with sodium alginate in ethanol under neutral conditions at room temperature. It is observed that in the presence of recyclable sodium alginate biocatalyst, highly pure chalcone with excellent yields in a very short time are obtained. The chalcone derivatives obtained are well characterized by UVDRS and FTIR techniques. The easily separable Na-alginate biocatalyst acts as a Bronsted acid and may be reused up to five cycles.

1. Introduction

Green chemistry aims to prevent waste and generate substances with little or no toxicity to humans and the environment, thereby maximizing atom economy.[1] Nowadays, understanding to the increasing environmental pollution and its devastating effect on ecosystem, development of new protocols based on environmentally benign resources and chemical methods has fascinated considerable attention.[2] The heterogeneous catalysis has been developed as a useful tool because of higher purity of the products, simplicity of the separation, and recycling of the catalysts.[3] The appreciation of biopolymers like chitosan, cellulose, starch, wool, and alginates[4] arises from their environmental sustainability and easy availability. However, the use of such macromolecules in pure form, as heterogeneous catalysts, is of great importance owing to elimination of toxicity of metals, and their oxides, biodegradability, eco-friendly properties, and cost-effectively.[8,9] Sodium alginate acts as Bronsted acid in chemical transformations and additionally, the ability of sodium alginate for absorbing water, promotes its catalytic activity, especially when water is a byproduct of the reaction such as condensation reactions.[5–7] The chemistry of chalcone has generated intensive scientific studies throughout the world. The presence of a reactive α, β unsaturated ketone functional group in chalcone is found to be responsible for their antimicrobial activity.[8–13] In the Claisen–Schmidt reaction, the concentration of alkali used, usually ranges between 10% and 60% or its carried out under strong acidic conditions.[14–16] The reaction is carried out at about 50 C for 12–15 h or at room temperature for almost 1 week. Also, the Claisen–Schmidt reaction was improved by using various catalyst systems.[17,18] Herein we report a one-pot green chemistry reaction method by using sodium alginate biopolymer as a natural source of base for the formation of high-purity chalcone derivatives. Several chalcone were prepared by just magnetic stirring the equimolar quantities of the appropriate methyl ketone and different aryl aldehydes in the presence of sodium alginate in ethanol at room temperature.

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2. Experimental Section

Melting points were measured on an Electro thermal melting-point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Shimadzu Fourier transform (FT)–IR 8101 PC IR spectrophotometer.

2.1. General Procedure

A mixture of the aromatic methyl ketone (5 mmol), aromatic aldehyde (5 mmol) was dissolved in 5 mL ethanol, 15 mol% of sodium alginate was added as the catalyst, and the reaction mixture was stirred at room temperature on a magnetic stirrer for the appropriate time (**Scheme 1**).

2.2. Optimization of Reaction Conditions

2.2.1. Screening of Catalyst and its Amount

A control reaction experiment was performed without catalyst resulting in low yields of products and high reaction time (**Table 1**). Various catalysts such as acetic acid, tartaric acid, chitosan, starch, sodium alginate, and reaction without catalyst were tested and compared with respect to yields of the product under magnetic stirring. The control reaction in the presence of sodium alginate afforded the product quickly with higher yield in ethanol under magnetic stirring.

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