International Journal of Research in Pharmaceutical sciences and Technology

Harnessing medicinal plant phytochemicals: unveiling pharmacological potential and novel drug delivery strategies

Buduru Gowthami[1] and Hima Bindu K[2]

[1]Department of Pharmaceutics, Annamacharya College of Pharmacy, Rajampet, Y.S.R Cuddapha-516126, India
[2]Department of Pharmaceutical Analysis, Anurag Group of Institutions, Ghatkesar, RR district-606603, Telanagan, India.

ABSTRACT

The significant progress in the field of anticancer research has spurred a growing interest in bioactive compounds with potential pharmacological properties. One well-established challenge in utilizing these natural bioactives is their inherent low solubility, leading to limited bioavailability and difficulties in formulating effective drug delivery strategies to specific target sites. In response to this challenge, this review provides a comprehensive overview of the latest advancements in the development of innovative drug delivery systems. Our analysis focuses on published data related to key plant secondary metabolites known for their potent anticancer potential, specifically the flavone, isoflavone, and stilbene groups, which have been successfully formulated using novel drug delivery systems. While the precise mechanisms of action for these selected natural compounds remain a subject of ongoing investigation, their anticancer effects are undeniable. Consequently, current research efforts are primarily dedicated to identifying these bioactive compounds' most effective delivery systems. Recent studies aim to elucidate the exact mechanisms of action and therapeutic benefits of these compounds and address the crucial issue of designing suitable natural compound delivery systems capable of efficiently transporting therapeutic doses to the intended target sites. This multifaceted approach underscores the ongoing commitment to advancing the field of anticancer research and improving the delivery of bioactive compounds with promising anticancer potential.

Keywords: *Natural extracts; Bioactive; Anti-cancer; Anti-viral; Nanoparticles; Drug delivery systems.*

ISSN: 2581-9143
Review Article

Corresponding Author
Name: Buduru Gowthami
Email: bindu.maroju@gmail.com

Article Info
Received on: 08-10-2023
Revised on: 20-10-2023
Accepted on: 28-10-2023
DOI: https://doi.org/10.33974/ijrpst.v3i4.344

INTRODUCTION

Bioactive compounds derived from natural sources, such as plants, microorganisms, and animals, have played a vital role in traditional medicine for millennia. However, the practical application of these natural compounds is often hindered by challenges related to their limited oral bioavailability and restricted systemic distribution. Several physical, chemical, and metabolic factors influence these limitations, including solubility, susceptibility to degradation in gastrointestinal conditions (such as varying pH levels and enzymatic activity), brief residence time in the stomach, potential interactions with other nutrients, and absorption rates in the intestine [1, 2].

In the context of natural bioactive compounds with anticancer properties, their low bioavailability poses a significant obstacle to their effectiveness as anticancer therapies. Researchers are continually making strides in addressing this issue and have proposed various solutions. However, significant challenges remain. One promising avenue involves the incorporation of these bioactives into carriers, which offers a potential solution without altering their pharmacological properties through chemical modifications. One such promising approach involves the development of nanoparticle systems designed to encapsulate natural bioactive compounds. These nanoparticles can serve as protective vehicles, facilitating the safe transport of bioactives to their intended target sites within the body. This strategy holds considerable potential for overcoming the limitations associated with the bioavailability and systemic delivery of bioactive compounds of natural origin. This review seeks to provide an overview of

recent advancements in critical areas pertaining to the biomedical utilization of natural products with anticancer properties and the adoption of novel drug delivery systems as carriers for their efficient delivery.

In recent anticancer research, a prominent focus has been on exploring the impact of phytochemicals on malignant cells and their potential to inhibit the growth and division of transformed cells. The understanding that exposure to certain natural compounds, whether through dietary sources or pharmaceuticals, can modulate, prevent, delay, or arrest the process of carcinogenesis has become a well-established approach in contemporary anticancer drug discovery. Plants, rich sources of primary and secondary metabolites with diverse properties, offer a vast array of possibilities for biomedical applications. Consequently, a significant proportion of crucial anticancer pharmaceuticals in use today are either derived from plant bioactives or are structurally related derivatives. The sheer complexity and diversity of natural plant compounds in terms of their structures and characteristics make it challenging to devise a concise classification scheme for their systematic presentation and evaluation.

In accordance with existing literature [3, 4], this study categorizes plant bioactives based on their chemical structures into distinct major groups, including vitamins, polyunsaturated fatty acids, carotenoids, polyphenols, organosulfur compounds, selenium compounds, alkaloids, and miscellaneous compounds. Numerous representatives from these groups are undergoing comprehensive assessment in various in vitro and in vivo experiments to ascertain their potential anticancer properties [5-11]. For instance, garlic and its sulfur-containing compounds, such as diallyl disulfide, have demonstrated significant inhibitory effects on mammary cancer in animal models, notably rats, and have shown promise in suppressing the growth of human breast cancer cells. Furthermore, these effects were potentiated when selenium-enriched garlic or organoselenium compounds were introduced [6, 8, 9]. Similarly, several polyphenolic compounds have emerged as subjects of intense interest in the realm of anticancer research.

Natural extracts with Pharmacological activity

Green tea catechins, notably (-)-epigallocatechin-3-gallate, are recognized as bioactive compounds with a multitude of beneficial effects on human health, including potential benefits in combating various cancers, heart disease, and liver disorders. These catechins have also demonstrated synergistic anticancer properties when combined with other anticancer pharmaceuticals or nonsteroidal anti-inflammatory drugs (NSAIDs) when tested against different human cancer cell lines [10]. Alkaloids, a class of alkaline heterocyclic nitrogen-containing natural compounds, are among the abundant plant metabolites originally produced as toxic substances by plants but exhibiting significant anticancer potential in humans. Well-known alkaloids like vinblastine, topotecan, taxol, and vincristine are integral components of established clinical anticancer therapies. Moreover, alkaloids such as brucine, cryptolepine, or noscapine continue to be evaluated for their antineoplastic and apoptotic capabilities [11]. It's noteworthy that many of today's leading anticancer pharmaceuticals are either derived from plants or are closely related derivatives, and the quest for improved and more effective anticancer treatments remains ongoing. Plant-derived compounds hold particular appeal as anticancer agents due to their natural availability, oral administration suitability (including dietary intake), generally well-tolerated nature, and non-toxicity towards healthy cells (with some exceptions like cyanogenic glycosides, lectins, saponins, and taxanes). Nevertheless, the primary challenge in utilizing natural plant compounds as anticancer drugs lies in their limited success in clinical trials, primarily attributable to issues related to bioavailability, dosage, and delivery [12-14].

To enhance their bioavailability and anticancer efficacy, various drug delivery formulations have been developed, including nanosuspensions, nanoparticles (such as solid lipid nanoparticles, gold nanoparticles, and polymeric nanoparticles), liposomes, exosomes, niosomes, implants, and cell-based systems [15-23]. These novel delivery systems substantially improve active agent delivery by enhancing targeting capabilities, bioavailability, intracellular concentration, stability, and efficacy while concurrently mitigating toxicity and adverse side effects. The polyphenol group, a diverse class of plant secondary metabolites, exhibits remarkable anticancer potential attributed to their unique biological properties, including antioxidant activity, inhibition of cancer cell growth, proapoptotic effects, and cytotoxicity [14]. Prominent members of this group, such as flavonoids, tannins, curcumin, resveratrol, and gallocatechin, have garnered significant attention in anticancer research [10, 17, 19, 24-26].

For instance, curcumin, derived from turmeric, has gained widespread recognition not only as a culinary spice but also as one of the most extensively investigated polyphenolic compounds in recent anticancer research. It has demonstrated cytotoxicity against various cancer types, including hepatoma, breast cancer, lung cancer, prostate cancer, melanoma, neck and head cancers, and more [27-30]. Another well-known polyphenol, resveratrol, is studied both in isolation and in combination with other bioactive compounds and chemotherapeutics due to its synergistic chemopreventive potential in cancer. In this review, we have selected several intriguing representatives from the polyphenol group, including quercetin, genistein, curcumin, and

resveratrol, and examined current published data regarding their encapsulation in nanoparticles or exosomes for their anticancer properties. While the exact mechanisms of action for these four compounds remain to be fully elucidated, their described anticancer effects are likely attributable to their modulation of cellular and signaling pathways, transcription factors, proteins, enzymes, and growth factors.

Novel bioactive delivery systems

Recent advances in nanoparticle (NP) formulations have emerged as a promising strategy to enhance the bioavailability and specific localization of bioactive natural compounds within tumor sites [31]. Moreover, the versatility of NP design allows for the incorporation of various materials and structures, enabling controlled and targeted drug delivery while improving bioavailability and pharmacokinetics [32]. Nanoparticles, owing to their diminutive size, offer an extensive surface area, which can augment solubility, elevate bioavailability, enhance stability by safeguarding the active substance from enzymatic degradation, and prolong circulation time [34]. Nanoparticles typically involve the loading of active compounds into different matrices or encapsulating them within cavities, resulting in particles ranging from 1 to 1000 nanometers in size [35]. These Nanoparticles can encompass distinct components, including core constituents, therapeutic molecules, and surface modifiers for precise targeting [36]. The ability to create nanoparticles as both matrix-type particles (nanospheres) and cavity-loaded particles (nanocapsules) adds another dimension to drug design [37]. Various materials have been employed in NP production, including inorganic (metal-based or silicon-based), polymeric (such as polyesters, polysaccharides, and proteins), and lipid materials, with recent research exploring combinations of these materials [38]. Numerous bioactive polyphenols have already been successfully formulated into Nanoparticles, and ongoing research continues to expand this area. This review focuses on the most extensively investigated bioactive compounds that have been incorporated into NP formulations and assessed for their anticancer potential.

Curcumin, renowned for its anticancer and antioxidative properties, has garnered significant attention. Most NP formulations containing curcumin utilize biodegradable polymers and copolymers like chitosan, lipid nanosystems, MPEG-PCL copolymers, and PLGA. Additionally, hybrid inorganic-organic Nanoparticles have been explored, incorporating silver-containing micelles within polymers. Resveratrol-containing NP formulations are primarily based on biodegradable polymers like PEG-PLA systems and lipid nanosystems. However, resveratrol has also been studied in the context of anticancer activity after incorporation into inorganic mesoporous silica [39]. Strategies involving ligand attachment have been proposed to enhance the targeted delivery of resveratrol, such as attaching folic acid to target folate receptors [40] or employing the biotin-avidin system for improved targeting [41]. Quercetin-loaded Nanoparticles have mainly been designed to target breast cancer. These formulations have utilized various polymer assemblies, including PLA, PLGA, DSPE-PEG2000, and modified FITCDSPE-PEG2000. Targeted delivery has also been achieved by incorporating folic acid as a component in both inorganic silica particles and biodegradable polymers to target folate receptors [42]. Hyaluronic acid has been employed as it binds specifically to CD44, a glycoprotein overexpressed on the surface of various tumor cells [43]. Efforts have been made to target folate receptor-positive carcinomas with Nanoparticles containing genistein, which have been investigated for their activity in cervical carcinoma HeLa cell lines [45]. Additionally, attempts have been made to harness the anticancer potential of a combination of genistein and curcumin within nanostructured lipid carriers, particularly in prostate cancer cell lines [46].

Current trends and futuristic approaches

Cancer remains a major global health challenge, characterized by significant morbidity and mortality rates. Conventional anticancer treatments such as surgery, chemotherapy, and radiotherapy often entail high risks of poor outcomes, treatment unresponsiveness, relapse, or the development of drug resistance. Therefore, there is an urgent need for innovative modalities and approaches that can enhance treatment efficacy while minimizing adverse effects. Natural compounds derived from plants offer promise as potential anticancer agents, harnessing their synergistic protective effects through various mechanisms of action when combined with established anticancer drugs. These natural compounds possess both distinct advantages and challenges. Their pleiotropy, stemming from their ability to activate multiple biochemical pathways, is a significant asset. However, their low bioavailability presents a substantial limitation, resulting in insufficient plasma concentrations to elicit an anticancer response. The complexity increases when considering that low doses of these natural compounds, when consumed in conjunction with other plant-based compounds, can exhibit synergistic anticancer effects [47-52]. Consequently, predicting clinical outcomes following the administration of natural bioactive compounds remains a formidable task. For instance, while curcumin has garnered substantial scientific interest in recent years, its therapeutic effects remain somewhat elusive, often attributed to its low bioavailability. Hence, current research endeavors are not solely aimed at unraveling the precise mechanisms of action and potential therapeutic benefits but also at developing delivery systems capable of transporting adequate doses of bioactive compounds to their intended targets [53-58].

Currently, nanoparticles hold a prominent position in the quest for suitable drug delivery systems. However, earlier research has raised concerns regarding Nanoparticles, highlighting limitations such as complex manufacturing processes leading to elevated formulation costs, the use of toxic solvents and polyvinyl alcohol as stabilizers, potential immune responses, allergic reactions upon administration, and the possibility of incorporated drugs forming covalent bonds with NP polymers [59-64]. Moreover, toxicity concerns have emerged as a primary drawback associated with many synthetic nanoparticles. These challenges have prompted a growing interest in exosomes, naturally-derived nanoparticles, which appear promising for drug delivery. Nevertheless, the application of advanced formulations faces additional considerations, including scalability issues due to physical and chemical instability, material costs, the need for specialized equipment, and a skilled workforce in large-scale production [65-70]. These factors underscore the multifaceted nature of the pursuit of improved anticancer therapies and underscore the importance of addressing both therapeutic efficacy and safety in the development of novel drug delivery systems [70-85].

CONCLUSION

Despite the promising outcomes observed in experimental studies, including in vitro investigations and in vivo animal trials, our knowledge regarding the loading of specific drug delivery systems with drugs and their design as viable pharmaceutical formulations for human in vivo applications remains limited. As we move forward, future research endeavors will determine whether these challenges can be effectively surmounted. Additionally, this research will identify which types of delivery systems and natural bioactive compounds possess the requisite properties to potentially emerge as the next generation of innovative anticancer or antiviral agents.

REFERENCES

1. Li Z, Jiang H, Xu CM, Gu LW. A review: Using nanoparticles to enhance absorption and bioavailability of phenolic phytochemicals. Food Hydrocoll 2015; 43: 153-64.
2. Heleno SA, Martins A, Queiroz MJRP, Ferreira ICFR. Bioactivity of phenolic acids: Metabolites versus parent compounds: A review. Food Chem 2015; 173: 501-13.
3. Kinghorn AD, Su BN, Jang DS, Chang LC, Lee D, Gu JQ, et al. Natural inhibitors of carcinogenesis. Planta Med 2004; 70: 691- 705.
4. Mehta RG, Murillo G, Naithani R, Peng X. Cancer chemoprevention by natural products: How far have we come? Pharm Res 2010; 27: 950-61.
5. Lippman SM, Hawk ET. Cancer prevention: From 1727 to milestones of the past 100 years. Cancer Res 2009; 69: 5269-84.
6. Egharevba GO, Dosumu OO, Oguntoye SO, Njinga NS, Dahunsi SO, Hamid AA, Anand A, Amtul Z, Priyanka U. Antidiabetic, antioxidant and antimicrobial activities of extracts of Tephrosia bracteolata leaves. Heliyon. 2019 Aug 1;5(8).
7. Lu J-J, Bao J-L, Chen X-P, Huang M, Wang Y-T. Alkaloids isolated from natural herbs as the anticancer agents. ECAM 2012; 7- 19.
8. Gao C, Jiang X, Wang H, Zhao Z, Wang W. Drug metabolism and pharmacokinetics of organosulfur compounds from garlic. J Drug Metab Toxicol 2013; 4: 159-64.
9. Nicastro HL, Ross SA, Milner JA. Garlic and onions: Their cancer prevention properties. Cancer Prev Res (Phila) 2015; 8(3): 181-89.
10. Anand A, Komati A, Katragunta K, Shaik H, Nagendla NK, Kuncha M, Mudiam MK, Babu KS, Tiwari AK. Phytometabolomic analysis of boiled rhizome of Nymphaea nouchali (Burm. f.) using UPLC-Q-TOF-MSE, LC-QqQ-MS & GC–MS and evaluation of antihyperglycemic and antioxidant activities. Food Chemistry. 2021 Apr 16;342:128313.
11. Habli Z, Toumieh G, Fatfat M, Rahal ON, Gali-Muhtasib H. Emerging cytotoxic alkaloids in the battle against cancer: Overview of molecular mechanisms. Molecules 2017; 22: 250-7.
12. Amin A, Gali-Muhtasib H, Ocker M, Schneider-Stock R. Overview of major classes of plant-derived anticancer drugs. Int Journal Biomed Sci 2009; 5(1): 1-11.
13. Unnati S, Ripal S, Sanjeev A, Niyati A. Novel anticancer agents from plant sources. Chin J Nat Medicines 2013; 11(1): 16-23.
14. Greenwell M, Rahman P.K.S.M. Medicinal plants: Their use in anticancer treatment. Int J Pharm Sci Res 2015; 6(10): 4103-12.
15. Brannon-Peppas L, Blanchette JO. Nanoparticle and targeted systems for cancer therapy. Adv Drug Deliver Rev 2004; 56: 1649-59.
16. Bisht S, Feldmann G, Soni S, Ravi R, Karikar C, Maitra A. Polymeric nanoparticle-encapsulated curcumin ("nanocurcumin"): A novel strategy for human cancer therapy. J Nanobiotechnol 2007; 5: 3-12.
17. Hariprasad KS, Anand A, Rathod BB, Zehra A, Tiwari AK, Prakasham RS, Raju BC. Neoteric Synthesis and Biological Activities of Chromenopyrazolones, Tosylchromenopyrazolones, Benzoylcoumarins. ChemistrySelect. 2017 Nov 13;2(32):10628-34.

18. Oerlemans C, Bult W, Bos M, Storm G, Nijsen JFW, Hennink WE. Polymeric micelles in anticancer therapy: Targeting, imaging and triggered release. Pharm Res 2010; 27: 2569-89.

19. Hu B, Ting YW, Yang XQ, Tang WP, Zeng XX, Huang QR. Nanochemoprevention by encapsulation of (-)-epigallocatechin-3- gallate with bioactive peptides/chitosan nanoparticles for enhancement of its bioavailability. Chem Commun 2012; 48: 2421-3.

20. Aqil F, Munagala R, Jeyabalan J, Vadhanam MV. Bioavailability of phytochemicals and its enhancement by drug delivery systems. Cancer Lett 2013; 334(1): 133-41.

21. Watkins R, Wu L, Zhang C, Davis RM. Natural product-based nanomedicine: Recent advances and issues. Int J Nanomed 2015; 10: 6055-74.

22. Pérez-Herrero E, Fernández-Medarde A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. Eur J Pharm Biopharm 2015; 93: 52-79.

23. Palazzolo S, Bayda S, Hadia M, Caligiuri I, Corona G, Toffoli G, et al. The clinical translation of organic nanomaterials for cancer therapy: A focus on polymeric nanoparticles, micelles, liposomes and exosomes. Curr Med Chem 2017; 24: 1-44.

24. Komati A, Anand A, Shaik H, Mudiam MK, Babu KS, Tiwari AK. Bombax ceiba (Linn.) calyxes ameliorate methylglyoxal-induced oxidative stress via modulation of RAGE expression: identification of active phytometabolites by GC-MS analysis. Food & function. 2020;11(6):5486-97.

25. Farzaei MH, Bahramsoltani R, Rahimi R. Phytochemicals as adjunctive with conventional anticancer therapies. Curr Pharm Res 2016; 22(27): 4201-18.

26. Davatgaran-Taghipour Y, Masoomzadeh S, Farzaei MH, Bahramsoltani R, Karimi-Soureh Z, Rahimi R, et al. Polyphenol nanoformulations for cancer therapy: Experimental evidence and clinical perspective. Int J Nanomed 2017, 12: 2689-702.

27. Shih H, Pickwell GV, Quattrochi LC. Differential effects of flavonoid compounds on tumorpromoter-induced activation of the human CYP1A2 enhancer. Arch Biochem 2000; 373: 287-94.

28. Mendoza E, Burd R. Quercetin as a systemic chemopreventative agent: Structural and functional mechanisms. Mini Rev Med Chem 2011; 11: 1216-21.

29. Sak K. Site-specific anticancer effects of dietary flavonoid quercetin. Nutr Cancer 2014; 66: 177-93.

30. Murakami A, Ashida H, Terao J. Multitargeted cancer prevention by quercetin. Cancer Lett 2008; 269(2): 315-25.

31. Kurakula M, Patel DB, Patel B, Gorityala S, Basim P. Functionalized Nanocarriers for Drug delivery: Amalgam of Biopolymers and Lipids. J Nanomed. 2021;4(1):1037.

32. Khan F, Niaz K, Maqbool F, Ismail Hassan F, Abdokkahi M, Naqulapalli Venkata KC, et al. Molecular targets underlying the anticancer effects of quercetin: An update. Nutrients 2016; 8: 529- 35.

33. Pavan Kumar P, Siva B, Anand A, Tiwari AK, Vekata Rao C, Boustie J, Suresh Babu K. Isolation, semi-synthesis, free-radicals scavenging, and advanced glycation end products formation inhibitory constituents from Parmotrema tinctorum. Journal of Asian Natural Products Research. 2020 Oct 2;22(10):976-88.

34. Sarkar FH, Li Y. Mechanisms of cancer chemoprevention by soy isoflavone genistein. Cancer Metastasis Rev 2002; 21: 265-80.

35. Banerjee S, Li Y, Wang Z, Sarkar FH. Multi-targeted therapy of cancer by genistein. Cancer Lett 2008; 269: 226-42.

36. Li Q-S, Li C-Y, Li Z-L, Zhu H-L. Genistein and its synthetic analogs as anticancer agents. Antixancer Agents Med Chem 2012; 12: 271-81.

37. Yin D, Hao J, Jin R, Yi Y, Bodduluri SR, Hua Y, Anand A, Deng Y, Haribabu B, Egilmez NK, Sauter ER. Epidermal Fatty Acid–Binding Protein Mediates Depilatory-Induced Acute Skin Inflammation. Journal of investigative dermatology. 2022 Jul 1;142(7):1824-34.

38. Lee J-Y, Kim HS, Song Y-S. Genistein as potential anticancer agent against ovarian cancer. J Tradit Complement Med 2012; 2(2): 96-104.

39. Shah HG, Rathod V, Basim P, Gajera B, Dave RH. Understanding the impact of multi-factorial composition on efficient loading of the stable ketoprofen nanoparticles on orodispersible films using Box-Behnken Design. Journal of Pharmaceutical Sciences. 2022 May 1;111(5):1451-62.

40. Maheshwari R, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: A short review. Life Sci 2006; 78: 2081-7.

41. Strimpakos AS, Sharma RA. Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. Antioxid Redox Signal 2008, 10: 511-45.

42. Kurakula M, Basim P. Biopolymer-Lipid Hybrid Composites and their Advances in Bio-imaging and Drug Delivery. J Radiol Med Imaging. 2021;4(1):1041.

43. Davis CD, Ross SA. Evidence for dietary regulation of microRNAexpression in cancer cells. Nutr Rev 2008; 66: 477-82.

44. Anand A, Priyanka U, Nayak VL, Zehra A, Babu KS, Tiwari AK. Nutritional composition and antioxidative stress properties in boiled tuberous rhizome of Neel Kamal (Nymphaea nouchali Burm. f.). Indian Journal of Natural Products and Resources (IJNPR)[Formerly Natural Product Radiance (NPR)]. 2019 Jun 9;10(1):59-67.

45. Zaman MS, Chauhan N, Yallapu MM, Gara RK, Maher DM, Kumari S, et al. Curcumin nanoformulation for cervical cancer treatment. Sci Rep 2016; 6: 20051-9.

46. Xie M, Fan D, Zhao Z, Li Z, Li G, Chen Y, et al. Nanocurcumin prepared via supercritical: Improved anti-bacterial, anti-oxidant and anti-cancer effcacy. Int J Pharm 2015; 496(2): 732-40.

47. Srujana MS, Thota RS, Anand A, Anusha K, Zehra A, Prasad K, Babu KS, Tiwari AK. Raphanus sativus (Linn.) fresh juice priming moderates sucrose-induced postprandial glycemia as well as postprandial glycemic excursion in rats.

48. Aluyen JK, Ton QN, Tran T, Yang AE, Gottlieb HB, Bellanger RA. Resveratrol: Potential as anticancer agent. J Diet Suppl 2012; 9(1): 45-6.

49. Basim P, Ajjarapu S, Kurakula M. Conductive polymers for drug and bioactives delivery. InSmart Polymer Nanocomposites 2023 Jan 1 (pp. 263-278). Elsevier.

50. Varoni EM, Lo Faro AF, Sharifi-Rad J, Iriti M. Anticancer mechanisms of resveratrol. Front Nutr 2016; 3: 8-16.

51. Diaz-Gerevini GT, Repossi G, Dain A, Tarres MC, Das UN, Eynard AR. Benefcial action of resveratrol: How and why? Nutrition 2016; 32: 174-8.

52. ailakshmi AS, Anand A, Madhusudana K, Nayak VL, Zehra A, Babu KS, Tiwari AK. Diospyros melanoxylon (Roxb.): A tribal fruit that maintains euglycemic state after consumption and cools oxidative stress. Indian Journal of Natural Products and Resources (IJNPR)[Formerly Natural Product Radiance (NPR)]. 2018 Dec 28;9(3):194-203.

53. Lu M, Xing H, Xun Z, Yang T, Ding P, Cai C, et al. Exosome-based small RNA delivery: Progress and prospects. Asian J Pharm Sci 2018; 13(1): 1-11.

54. Record M, Subra C, Silvente-Poirot S, Poirot M. Exosomes as intercellular signalosomes and pharmacological effectors. Biochem Pharmacol 2011; 81(10): 1171-82.

55. Huang Q, Yu H, Ru Q. Bioavailability and delivery of nutraceuticals using nanotechnology. J Food Sci 2010; 75(1): R50-7.

56. Mallesh K, Pasula N, Kumar Ranjith CP. Piroxicam proliposomal gel: a novel approach for tropical delivery. Journal of Pharmacy Research. 2012;5(3):1755-63.

57. Mozafari MR, Khosravi-Darani K, Gokce Borazan G, Cui J, Pardakhty A, Yurdugul S. Encapsulation of food ingredients using nanoliposome technology. Int J Food Prop 2008; 11: 833-44.

58. Nam J-S, Sharma AR, Nguyen LT, Chakraborty C, Sharma G, Lee S-S. Application of bioactive quercetin in oncotherapy: From nutrition to nanomedicine. Molecules 2016; 21: 108-13.

59. Priyanka U, Anand A, Bhargavi K, Zehra A, Tiwari AK. Presence of postprandial antidysmetabolic and antioxidative stress properties in aqueous methanol extract of seeds and tuber of aquatic food plant Nymphaea nouchali (Burm. f.). Cogent Food & Agriculture. 2016 Dec 31;2(1):1249172.

60. Ferrari M. Cancer nanotechnology: Opportunities and challenges. Nat Rev Cancer 2005; 5(3): 161-71.

61. Kurakula M, Gorityala S, Basim P, Sun M, Mannem C. Rationalizing Nanodeliverables for Effective L-Asparaginase Delivery in Chemotherapy: Update 2020. Cancer Sci. Res. 2021;4:1-7.

62. Summerlin N, Qu Z, Pujara N,Sheng Y, Jambhrunkar S, McGuckin M, et al. Colloidal mesoporous silica nanoparticles enhance the biologicalactivity of resveratrol. Colloids Surf B Biointerfaces 2016; 144: 1-7.

63. Komati A, Anand A, Nagendla NK, Madhusudana K, Mudiam MK, Babu KS, Tiwari AK. Bombax ceiba calyx displays antihyperglycemic activity via improving insulin secretion and sensitivity: Identification of bioactive phytometabolomes by UPLC-QTof-MS/MS. Journal of Food Science. 2022 Apr;87(4):1865-81.

64. Bu L, Gan L-C, Guo X-Q,Chen F-Z, Song Q, Qi-Zhao, et al. Trans-resveratrol loaded chitosan nanoparticles modified with biotin and avidin to target hepatic carcinoma. Int J Pharm 2013; 452(1- 2): 355-62.

65. Sarkar A, Ghosh S, Chowdhury S, Pandey B, Sil PC. Targeted delivery of quercetin loaded mesoporous silica nanoparticles to the breast cancer cells. Biochim Biophys Acta 2016; 1860(10): 2065- 75.

66. Hu X, Ning P, Zhang R, Yang Y, Li L, Xiao X. Anticancer effect of folic acid modified tumor-targeting quercetin lipid nanoparticle. Int J Clin Exp Med 2016; 9(9): 17195-202.

67. Deepthi S, Anusha K, Anand A, Manasa A, Babu KS, Mudiam MK, Tiwari AK. Micronutrients and phytochemicals content in various rice (Oryza sativa Linn.) samples control carbohydrate digestion

variedly and present differential antioxidant activities: an in vitro appraisal.

68. Aruffo A, Stamenkovic I, Melnick M, Underhill CB, Seed B. CD44 is the principal cell surface receptor for hyaluronate. Cell 1990; 61(7): 1303-13.

69. Anand A, Priyanka U, Madhusudana K, Nayak VL, Zehra A, Babu KS, Tiwari AK. Administration of roasted barley and roasted horse gram powders pacified chronic sucrose-induced dysglycemia and dyslipidemia in rats and exerted In Vitro potent antioxidative stress effect. Pharmacognosy Magazine. 2018;14(59s).

70. Anusha K, Anand A, Babu KS, Tiwari AK. Bombax ceiba calyces regulate carbohydrate and lipid digesting enzyme's actions, display insulin sensitizing and antioxidant activities in vitro: A nutritional and phytochemicals examination.

71. Vecchione R, Quagliariello V, Calabria D, Calcagno V, De Luca E, Iaffaioli RV, et al. Curcumin bioavailability from oil in water nanoemulsions: In vitro and in vivo study on the dimensional, compositional and interactional dependence. J Control Release 2016; 233: 88-100.

72. Wan K, Sun L, Hu X, Yan Z, Yonghong Z, Zhang X, et al. Novel nanoemulsion based lipid nanosystems for favorable in vitro and in vivo characteristics of curcumin. Int J Pharm 2016; 504(1-2): 80-8.

73. Kumar TK, Siva B, Anand A, Anusha K, Mohabe S, Reddy AM, Le Devehat F, Tiwari AK, Boustie J, Babu KS. Comprehensive Lichenometabolomic Exploration of Ramalina conduplicans Vain Using UPLC-Q-ToF-MS/MS: An Identification of Free Radical Scavenging and Anti-Hyperglycemic Constituents. Molecules. 2022 Oct 9;27(19):6720.

74. Sarika PR, James NR, Kumar PR, Raj DK. Galactosylated alginatecurcumin micelles for enhanced delivery of curcumin to hepatocytes. Int J Biol Macromol 2016; 86: 1-9.

75. Kurakula M, Gorityala S, Patel DB, Basim P, Patel B, Kumar Jha S. Trends of chitosan based delivery systems in neuroregeneration and functional recovery in spinal cord injuries. Polysaccharides. 2021 Jun 15;2(2):519-37.

76. Gong C, Deng S, Wu Q, Xiang M, Wei X, Li L, et al. Improving antiangiogenesis and anti-tumor activity of curcumin by biodegradable polymeric micelles. Biomaterials 2013; 34(4): 1413-32.

77. Bhatt J, Shah H, Basim P, Morris K, Haware R. In Structure–Mechanics Study of Cocrystals to Optimize Tablet Size. InNIPTE Conference 2018.

78. Egharevba GO, Dosumu OO, Oguntoye SO, Njinga NS, Dahunsi SO, Hamid AA, Anand A, Amtul Z, Priyanka U. Corrigendum to "Antidiabetic, antioxidant and antimicrobial activities of extracts of Tephrosia bracteolata leaves"[Heliyon 5 (8)(August 2019) e02275]. Heliyon. 2019 Sep 1;5(9).

79. [79] Naksuriya O, Shi Y, van Nostrum CF, Anuchapreeda S, Hennink WE, Okonogi S. HPMA-based polymeric micelles for curcumin solubilization and inhibition of cancer cell growth. Eur J Pharm and Biopharm 2015; 94: 501-12.

80. Liu J, Xu L, Liu C, Zhang D, Wang S, Deng Z, et al. Preparation and characterization of cationic curcumin nanoparticles for improvement of cellular uptake. Carbohydr Polym 2012; 90(1): 16- 22.

81. Bakhaidar RB, Naveen NR, Basim P, Murshid SS, Kurakula M, Alamoudi AJ, Bukhary DM, Jali AM, Majrashi MA, Alshehri S, Alissa M. Response Surface Methodology (RSM) Powered Formulation Development, Optimization and Evaluation of Thiolated Based Mucoadhesive Nanocrystals for Local Delivery of Simvastatin. Polymers. 2022 Nov 28;14(23):5184.

82. Srujana MS, Thota RS, Anand A, Anusha K, Zehra A, Prasad K, Babu KS, Tiwari AK. Raphanus sativus (Linn.) fresh juice priming moderates sucrose-induced postprandial glycemia as well as postprandial glycemic excursion in rats.

83. Cao Y, Gao M, Chen C, Fan A, Zhang J, Kong D, et al. Triggeredrelease polymeric conjugate micelles for on- demand intracellular drug delivery. Nanotechnology 2015; 26(11): 115101.

84. Basim P, Gorityala S, Kurakula M. Advances in functionalized hybrid biopolymer augmented lipid-based systems: A spotlight on their role in design of gastro retentive delivery systems. Archives of Gastroenterology Research. 2021 Mar 2;2(1):35-47.

85. Guo W, Li A, Jia Z, Yuan Y, Dai H, Li H. Transferrin modified PEG-PLA-resveratrol conjugates: In vitro and in vivo studies for glioma. Eur J Pharmacol 2013; 718(1-3): 41-7.

86. Sun M, Nie S, Pan X, Zhang R, Fan Z, Wang S. Quercetinnanostructured lipid carriers: Characteristics and anti-breast cancer activities in vitro. Colloids Surf B Biointerfaces 2014; 113: 15-24.