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ANTICANCER POTENTIALS OF INDIAN MADDER (RUBIA CORDIFOLIA L.):AN OVERVIEW

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Abstract
Rubia cordifolia is used as an age-old drug for cancer remedies. Even today, the potential activity of the plant is identified in various cell lines. The anthraquinones, flavonoids, etc are the compounds responsible for its anti-proliferating properties. It is believed that the possible mechanism behind the anti-proliferation is inhibition of DNA synthesis. The anthaquinone moiety, rubiadin, is found to be the most identified anticancer compound in the form of RA series. The recent advancement in biogenic nanoparticles using R. cordifolia was also found to be very effective in cancer treatment. Further clinical studies are needed before using this drug for modern pharmacopeia. The review article is intended to give an overall view of this magnificent plant in the treatment of cancer

Keywords: Rubia cordifolia, cancer, cell line, medicine,anti-cancer

Introduction

From time immemorial medicinal plants have played an integral part in the well-being of humans. Plants contain a vast array of phytochemicals with diverse biological activities. The medicinal activities of plants depend on various genetic as well as environmental factors associated with each plant species. The traditional systems of medicines and the indigenous practices of using plant-based remedies, provide a rich source for discovering potential anticancer plants and compounds. R. cordifolia is one such plant that has many medicinal attributes and has been used in traditional as well as modern medicine.

It is a well-known fact that Rubia cordifolia (Indian Madder) has an immense ability to cure blood-related ailments. Even though, the most valued part is the root, the curative properties of other parts are also well explained. As per Sivarajan and Balachandran (1994), the roots can be used as a rejuvenating tonic.It can improve skin luster and hence is used in many skin- tone improving fairness creams and beauty therapies. It is used to treat intestinal ulcers (Prajapathi and Kumar, 2003), respiratory illness, and many menstrual difficulties The oil extract of whole plant is used in the treatment of eczema (Maitreya, 2015). Urinogenital disorders, piles, skin diseases, etc… are treated with dried stem powder (Khare, 2004). The leaf is also used in traditional medicine to cure fever, stomachache, and dysentery. The decoction of leaves and stems is used as vermifuge. Fruits can lower body temperature.
The plant R. cordifolia, though widely used in medication, its distribution is restricted to hilly tracks only. The endemic distribution made this plant unfamiliar to the populace of the modern world or even neglected where it flourishes well (Priya and Siril, 2013). Even though the demand exceeds its

production, region-wise,the plant is overlooked as a weed. So proper attention should be given to such plants with lots of medicinal properties.

Phytocompounds and its potent anti-cancer activity

As with other plant species, R. cordifolia, commonly known as Indian Madder, is enriched with numerous secondary metabolites. The amount and action of these metabolites may vary within the plant species, depending on the habitat, age of the plant, season of collection, etc. As per the traditional knowledge, the plant is highly useful in the treatment of cancer like leukemia.

The chemical composition of the plant is unaccountable and every day new varieties of bio-compounds are being identified. Most of these compounds have therapeutic effects and the plant as such now used in modern pharmacies as an agent to eliminate malignant tumors, cancer, etc… Research suggests that compounds like anthraquinones and flavonoids, which have shown anticancer effects in various studies. However, more research is needed to fully understand its mechanism of action and potentiality for clinical use in cancer therapy.

R. cordifolia can be considered the most extensively studied plant for its anti-cancer activities. Both in vitro and in vivo bio-assays on animal models revealed the potency of this plant in curing cancerous growth. Various fractions identified in the extracts of Rubia exhibit its anti-proliferative activity by inhibiting DNA synthesis.The compounds like rubiadin, purpurin, mollugin, and quinones. RA series(Rubiadin A) RC-18 (Rubiadin C), S-180, alkyl ether and ester derivatives of RA-V, RA-700, and the cyclic hexapeptides are used against carcinoma, melanoma, and leukemia (Itokawa et al., 1984 a &1984b; Kato et al., 1987; Hamanaka et al., 1987; Tripathi and Shukla, 1998; Itokawa and Saitou, 1992; Itokawa et al., 1992; Shoemarker et al., 2005; Kintzios, 2006).The efficacy of root extract on larynx carcinoma (Hep-2) cell line and cervical cancer cell line (HeLA) of human was proved during cell line study (Patel et al., 2011; Patel et al., 2011; Tiwari et al., 2012;) The root extracts showed cytotoxicity towards human carcinoma cell lines like colon carcinoma (HT-29), breast carcinoma [(MCF-7) (Aditya et al., 2013, Mughees et al., 2016; Okhtia, et al., 2020), and liver carcinoma (HepG2), MDA-MB-231 (Barlow et al., 2015).

The quinones and RC-18 showed the antiproliferative action against P388 leukemia, L1210, L5178Y, B16 melanoma (Adwankar and Chitnis, 1980; 82); S-180 and the cyclic hexapeptide against leukemia by interacting with the protein synthesis via blocking the peptidyl tRNA translocation (Morita et al., 1993). Significant nasopharynx carcinoma, P388 lymphocytic leukemia, and MM2 mammary carcinoma cells (Itokawa et al., 1984c96) inhibition was shown by the alkyl ether and ester derivative of RA-V. RA-700 was proven to be active against lymphoid leukemia (P388) and L1210 leukemia (Kato et al., 1987; Hamanataka et al., 1987). Similarly, the mollugin is a chemotherapeutic agent forthe inhibition of oral squamous cell carcinoma via the upregulation of HO-1 and Nrf2 pathways and the downregulation of NF- κB104 (Lee et al., 2013) The mito-depressive effect and subsequent apoptosis process was achieved through the elevation of reactive oxygen species generation on Hep-2 cell line (Shilpa et al., 2012).

The anti-cancerous activity against human leukemia cell lines and human histolytic lymphoma cell lines was also well established (Patel et al., 2010). The methanolic fraction was proved to be effective against HepG32 cell lines (Patel et al., 2013).The ethanolic root extracts was found to have significant activity against hepatocellular carcinoma cell lines (HepG2), breast cancer cell line (MCF-7), and pancreatic carcinoma cell line (BxPC-3) (Okhti et al., 2020). Previously Tripathi and Shukla (1998) identified the anti-proliferative action of Rubia extracts on epidermal carcinoma cell lines (A-431) and on fibroblast cell lines (3T3). The fraction inhibited the incorporation of [3H]-thymidine in a dose dependent manner. It also inhibited phorbol 12-myristate 13-acetate induced expression of c-fos genes in A431 cell lines.

The green nanoparticles synthesized using R. cordifolia have been investigated for their ability to deliver anticancer agents effectively to tumor cells. Recently, the cytotoxic activity of ZnO and CeO2 NPs synthesized from the Rubia leaf extracts showed its activity against a human osteosarcoma cell line MG-63 (Sisubalan et al., 2018). It is also shown anti-proliferation against B16F10 (melanoma), and A431 (carcinoma) cell lines (Chandraker et al., 2022).

Mechanism of action of Anthraquinones

Anthraquinone derivatives from Rubia cordifolia is well known for its anticancer activity, due to the peculiar planar tricyclic structure that can target at the molecular level. The bio-active compounds like alizarin, mollugen and cyclic hexapeptides are those compounds that can interfere with cancer cell signaling pathways and inhibit the vital processes like protein synthesis and DNA replication. Mechanistically, these compounds inhibit cancer progression by targeting essential cellular proteins, and lead to programmed cell death. It is evident from previous report that these compounds can inhibit protein synthesis in various cell lines viz., cervix, larynx, breast, liver and colon (Patel et al., 2011). The programmed destruction of cancer cells by these compounds and the cross talk between signaling pathways involved in cancer development and progression has been identified (Tiwari et al., 2012; Balachandran et al., 2021). The compounds like mollugen directly interfere with the incorporation of [3H] thymidine and the expression of the c-fos gene, which is involved in cell proliferation (Adwankar et al., 1980). While cthe cyclic hexapeptides can bind to the 80S ribosome submit, thus inhibiting the binding of aminoacyl-tRNA and the translocation of peptidyl-tRNA, which are crucial steps in protein synthesis. It has also shown that these compounds can regulate multiple signaling pathways involved in cancer development. It has a potential inhibitor of potential JAK-STAT pathway and, beneficial for treating cancer involving this pathway. It is also reported to inhibit nasopharyngeal carcinoma proliferation.

Conclusion

Many of these compounds have been found to exhibit anticancer properties in laboratory studies. Researchers are interested in exploring these natural compounds as potential alternatives or supplements to conventional chemotherapy drugs. these compounds that may be less toxic to normalcells while still targeting cancer cells effectively. Moreover, the plant-derived compounds may offer new avenues for overcoming drug resistance mechanisms and improving treatment outcomes.

References

1. Aditya, V. S., Kumar, N. L., &Mokkapati, A. L. (2013). In vitro anti-cancer activities of few plant extracts against MCF-7 and HT-29 cell lines. Int J Pharma Sci, 3, 185-8.
2. Adwankar, M. K., & Chitnis, M. P. (1982). In vivo Anti-cancer activity of RC-18: A Plant Isolate from Rubia cordifolia, Linn, against a spectrum of experimental tumour models. Chemotherapy, 28(4), 291-293.
3. Adwankar, M. K., Chitnis, M. P., Khandalekar, D. D., &Bhadsavale, C. G. (1980). Anti-cancer activity of the extracts of Rubia cordifolia Linn.(NSC b668893). Indian J Exp Biol. 18: 102-109
4. Balachandran P, Ibrahim MA, Zhang J, Wang M, Pasco DS, Muhammad I. Crosstalk of Cancer Signaling Pathways by Cyclic Hexapeptides and Anthraquinones from Rubia cordifolia. Molecules. 2021 Jan 31;26(3):735. doi: 10.3390/molecules26030735. PMID: 33572569; PMCID: PMC7866972.
5. Barlow, R., Barnes, D. A., Campbell, A. M., Nigam, P. S., & Owusu-Apenten, R. K. (2015). Antioxidant, anticancer and antimicrobial, effects of Rubia cordifolia aqueous root extract. Journal of Advances in Biology & Biotechnology 5(1): 1-8,
6. Chandraker, S. K., Lal, M., Khanam, F., Dhruve, P., Singh, R. P., & Shukla, R. (2022). Therapeutic potential of biogenic and optimized silver nanoparticles using Rubia cordifolia L. leaf extract. Scientific reports, 12(1), 8831.

7. Hamanaka, T., Ohgoshi, M., Kawahara, K., Yamakawa, K., Tsuruo, T., &Tsukagoshi, S. (1987). A novel antitumor cyclic hexapeptide (RA-700) obtained from Rubiae radix. Journal of pharmacobio-dynamics, 10(11), 616-623.
8. Itokawa, H., Saitou, K., Morita, H., Takeya, K., & Yamada, K. (1992). Structures and conformations of metabolites of antitumor cyclic hexapeptides, RA-VII and RA-X. Chemical and pharmaceutical bulletin, 40(11), 2984-2989.
9. Itokawa, H., Takeya, K., Mori, N., Hamanaka, T., Sonobe, T., & Mihara, K. (1984). Isolation and antitumor activity of cyclic hexapeptides isolated from Rubiae radix. Chemical and pharmaceutical bulletin, 32(1), 284-290.
10. Itokawa, H., Takeya, K., Mori, N., Takanashi, M., Yamamoto, H., Sonobe, T., &Kidokoro, S. (1984). Cell growth-inhibitory effects of derivatives of antitumor cyclic hexapeptide RA-V obtained from Rubiae radix (V). GANN Japanese Journal of Cancer Research, 75(10), 929-936.
11. Itokawa, H., Yamamiya, T., Morita, H., & Takeya, K. (1992). New antitumour bicyclic hexapeptides, RA-IX and-X from Rubia cordifolia. Part 3. Conformation–antitumour activity relationship. Journal of the Chemical Society, Perkin Transactions 1, (4), 455-459.
12. Kato, T., Suzumura, Y., Takamoto, S., & Ota, K. (1987). Antitumor activity and toxicity in mice of RA-700, a cyclic hexapeptide. Anticancer Research, 7(3 Pt B), 329-334.
13. Khare, C. P. (2004). Encyclopedia of Indian medicinal plants: National Western therapy, Ayurvedic and another traditional usage, Botany. Springer.
14. Kintzios, S. E. (2006). Terrestrial plant-derived anticancer agents and plant species used in anticancer research. Critical reviews in plant sciences, 25(2), 79-113.
15. Lee YM, Auh QS, Lee DW, Kim JY, Jung HJ, Lee SH, Kim EC,Involvement of Nrf2-Mediated Upregulation of Heme Oxygenase-1 in Mollugin-Induced Growth Inhibition and Apoptosis in Human Oral Cancer Cells. Bio Med. Res. Int., 2013, 2013, e210604
16. Maitreya, B. B. (2015). An overview of Ethnomedicinal plants of Family Rubiaceae from Sabarmati River of Gujarat state, India. International Journal of Pharmacy & Life Sciences, 6(5).
17. Morita, H., Yamamiya, T., Takeya, K., Itokawa, H., Sakuma, C., Yamada, J., & Suga, T. (1993). Conformational recognition of RA-XII by 80S Ribosomes: a differential line broadening study in 1H NMR spectroscopy. Chemical and Pharmaceutical Bulletin, 41(4), 781-783.
18. Mughees M, Sharma Y, Ahmad J, Ahmad A (2016) Comparitive analysis of anticancer activity of Rubia cordifolia L. &Adultrant on MCF-7 cell and SCAR Marker Development. Int J Plant, Animal Environ Sci, 7: 70-79
19. Okhtia, Z. A., Al-Sudani, B. T., & Abdalah, M. E. (2020). Study the effect of Rubia cordifolia extract on different types of cancer cell lines and different microbial. Sys Rev Pharm, 11: 994-1000.
20. Patel, P.R,. Patel N.N.,, Suthar, M.P., Rajesh, K.S. & Patel, L.D. (2013) In vitro anti-cancer activity of Rubia cordifolia against HepG 32 Cell Line, Pharmagene, 1(1),-3.113.
21. Patel, P.R., Nagar. A.A., Patel, R.C., Rathod, D.K., &Patel ,V.R. (2011) In vitro anticancer activity of Rubia cordifolia against HELA and HEP-2 cell lines, Int. J. Pharm. Pharm. Sci., 3, 70-71.115.
22. Patel, P.R., Raval, B.P., Karanth, H.A., Patel, V.R., Potent antitumor activity of Rubia cordifolia, Int. J. Phytomed. 2, 2010, 44-46.114.
23. Prajapati, H. A., Patel, D. H., Mehta, S. R., & Subramanian, R. B. (2003). Direct in vitro regeneration of CurculigoorchioidesGaertn., an endangered anticarcinogenic herb. Current science, 84(6), 747-749.
24. Priya, M.D., & Siril, E. A. (2013). Pharmacognostic studies on Indian madder (Rubia cordifolia L.). Journal of pharmacognosy and Phytochemistry, 1(5), 112-119.
25. Shilpa, P. N., Sivaramakrishnan, V., & Devaraj, S. N. (2012). Induction of apoptosis by methanolic extract of Rubia cordifolia Linn in HEp-2 cell line is mediated by reactive oxygen species. Asian Pac J Cancer Prev, 13(6), 2753-2758.

26. Shoemaker, M., Hamilton, B., Dairkee, S. H., Cohen, I., & Campbell, M. J. (2005). In vitro anticancer activity of twelve Chinese medicinal herbs. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives, 19(7), 649-651.
27. Sisubalan, N, Ramkumar, V.S,; Arivalagan, P; Karthikeyan, C & Indira, K. (2018). Environmental Science and Pollution Research; Heidelberg, 25 (11) 10482-10492. DOI:10.1007/s11356-017-0003
28. Sivarajan, V. V., & Balachandran, I. (1994). Ayurvedic drugs and their plant sources. Oxford and IBH publishing house, Nes Delhi.
29. Tiwari, S., Upadhyaya, R., Shroti, R., & Upadhyaya, S. T. (2012). Rubia cordifolia root extract induces apoptosis in cancer cell line. Sci. Secure J, 1(2), 39-42.