International Journal of Current Research and Review
DOI: https://doi.org/10.31782/IJCRR.2023.151402

Research Article

IJCRR
Section: Healthcare

Curcumin - Bio Conjugates as Chemotherapeutics: A Computational Study

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ABSTRACT

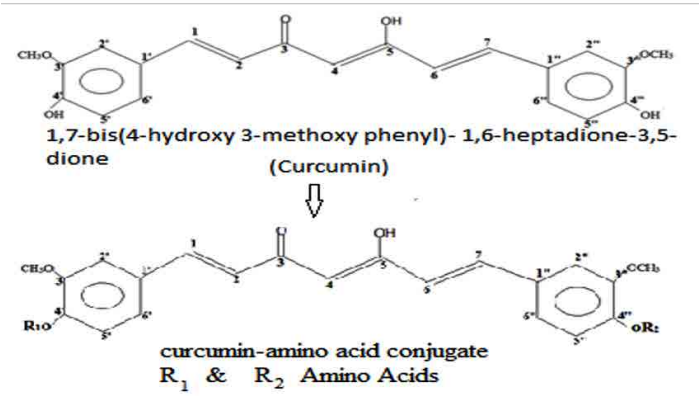
Introduction: Numerous studies have shown that curcumin possesses multifunctional pharmacological properties inducing apoptosis in a variety of tumor cells.

Aim/Objectve: It is very significant work to investigate the quantitative structure activity relationship (QSAR) and inhibition mechanisms of these curcumin-related compounds.

Method: QSAR studies of curcumin-amino acid bioconjugates have been carried out for their chemotherapeutic or anticancer activity against skin cancer cells. Based on molecular descriptor calculated by DRAGON software for QSAR, some key structural factors responsible for chemotherapeutic activity of these compounds were revealed.

Results: The results have provided some useful theoretical references for understanding the mechanism of action, designing new curcumin-related compounds with chemotherapeutic activity and were predicted their activities prior to synthesis.

Conclusion: The curcumin - glutamoyl derivative appeared to be the most effective compound when tested for antiproliferative potential.



Key Words: Curcumin, QSAR, Chemotherapeutics, Bio conjugates, Antiproliferative, Computation

INTRODUCTION

Turmeric contains several curcuminoids, including curcumin (Fig. 1), desmethoxycurcumin, and bisdesmethoxycurcumin, with curcumin being the major constituent.[1] Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a hydrophobic polyphenolic compound with antioxidant, anti-inflammatory, antimicrobial, antiviral, and chemotherapeutic or anticancer activities.[2,3,4] Curcumin inhibits proliferation and angiogenesis, induces apoptosis and cell cycle capture in a variety of tumor cell lines, and promotes tumor regression in a preclinical model.[5,6]

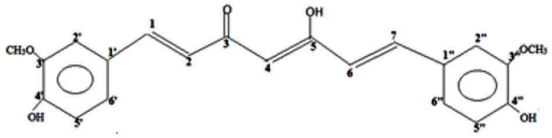


Figure 1

Curcumin,1,7-bis(4-hydroxy 3-methoxy phenyl)- 1,6-heptadione-3,5-dione or diferuloylmethane, is a yellow com-

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ISSN: 2231-2196 (Print) **ISSN:** 0975-5241 (Online)

Received: 16.06.2023 **Revised:** 28.06.2023 **Accepted:** 10.07.2023 **Published:** 30.07.2023

pound isolated from the dried rhizomes of plant Turmeric, and traditional medicine in India and other countries. However, a more detailed investigation about how the structural features of curcumin-amino acid conjugate compounds influence their anticancer activities and the inhibition mechanisms of these compounds remains largely unknown. Cancer is one of the most formidable afflictions in the world. Cancer may affect people at all ages, even fetuses, but risk for the more common varieties tends to increase with age. Using absorption and fluorescence spectroscopic methods, Kunwar et al.[7] showed that uptake of curcumin was significantly higher in cancer cells compared with normal cells. Curcumin is water insoluble, the poor solubility and wet ability of curcumin leads to poor dissolution and hence shows poor bioavailability. Absorption bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be rate determining step for appearance of medicinal effect, therefore efforts to increase dissolution of drug with limited water solubility is often needed. Many methods are available to improve the solubility, including salt formation, micronization bioactivity as well as bioavailability leads designing new structures with the variation in enhanced bioactivity as well as bioavailability depends on changes in chemical structure also.[12,13,14] Molecular docking studies related to the effect of curcumin conjugated to amino acids on the activated inhibition of polymerization of involved biomaterial in cell growth, proliferation and survival was very well studied.[15-20]

MATERIAL & METHOD

The Comprehensive Descriptor for Structural and Statistical Analysis (dragon) program was used in the calculation of molecular descriptors. Three types of descriptors were calculated; the constitutional, topological, and physicochemical molecular descriptors. The computational data used in this study were anticancer activity, IC (Inhibition Constant) and of a set of ten curcumin-amino, acid conjugates. The structural feature of substituted [R_1 and R_2 as substituent] curcumin is given in figure 2 and predicted biological activity of these compounds are listed in Table 1.

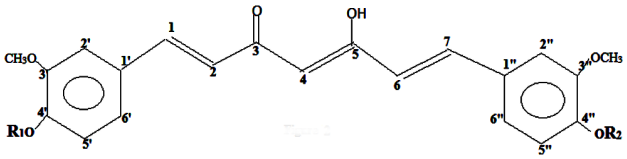


Figure 2

RESULTS

The antiproliferative property is due to its ability to induce apoptosis. The obtained results are presented in Table I in the form of inhibitory potential of the bio conjugates under consideration. Cytotoxicity potential of the compounds was also important to measure for safety and security so it was virtually done against the human endothelial lung cells.

Table 1: Name of curcumin-amino acid bioconjugates used in this study, their predicted activity for anticancer BCRP inhibition bioactivity.

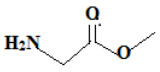
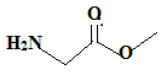
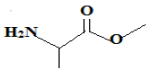
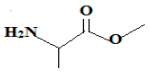
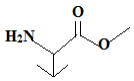
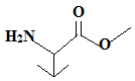
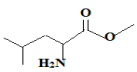
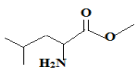
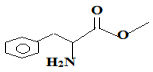
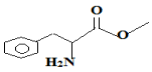
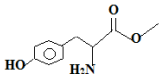
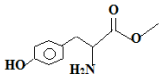
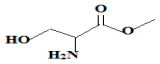
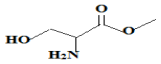
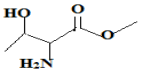
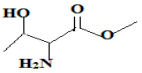
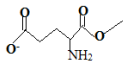
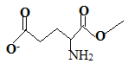
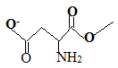
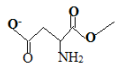
Amino Acid	R_1	R_2	Name of Conjugate	IC(µM)
Glycine			1,7-Bis(4-O-glycinoyl-3-methoxyphenyl)-1,4,6-heptatriene-5-ol-3-one	871.38
Alanine			1,7-Bis(4-O-alaninoyl-3-methoxyphenyl)-1,4,6-heptatriene-5-ol-3-one	317.43
Valine			1,7-Bis(4-O-valinoyl-3-methoxyphenyl)-1,4,6-heptatriene-5-ol-3-one	42.93
Leucine			1,7-Bis(4-O-leucinoyl-3-methoxyphenyl)-1,4,6-heptatriene-5-ol-3-one	307.46
Phenylalanine			1,7-Bis(4-O-phenylalaninoyl-3-methoxyphenyl)-1,4,6-heptatriene-5-ol-3-one	226.37
Tyrosine			1,7-Bis(4-O-tyrosinoyl-3-methoxyphenyl)-1,4,6-heptatriene-5-ol-3-one	210.45

Table 1: ***(Continued)***

Amino Acid	R_1	R_2	Name of Conjugate	IC(μM)
Serine			1,7-Bis(4-O-serinoyl-3-methoxyphenyl)-1,4,6-heptatriene-5-ol-3-one	407.78
Threonine			1,7-Bis(4-O-threoninoyl-3-methoxyphenyl)-1,4,6-heptatriene-5-ol-3-one	310.23
Glutamate			1,7-Bis(4-O-glutamatoyl-3-methoxyphenyl)-1,4,6-heptatriene-5-ol-3-one	1070.67
Aspartate			1,7-Bis(4-O-aspartatoyl-3-methoxyphenyl)-1,4,6-heptatriene-5-ol-3-one	1020.12

DISCUSSION

Appreciable disparity in the chemical/biological activities in these highly related compounds warranted a systematic quantitative structure-activity relationship (QSAR) to know their antioxidant, anti-HIV, antimelnoma and other anti-effects and it was done by reference study of molecules having the similar structural and electronic properties. The computation of statistical analysis was done by correlating the physicochemical parameters with the chemical and biological activities and is presented in the Table 1. All the tested compounds have anticancer activities comparable to those of curcumin against targeted cancer cell lines. It is obvious from Table 1 that the IC value is comparable with increasing chain length of the substituent on the hydroxyl oxygen atom.

CONCLUSION

The computational parameters about the compounds for QSAR, Chain of chemical reactions on cell division as signaling pathways and network complexity are the aspects by which the design of these bio-conjugates is done and these are also established for the diseases under consideration. The development of curcumin substituted compounds evidently increases the *in vivo* biological activities and it was well established by advances in the drug discovery. They could also increase the efficiency of classical chemotherapeutic drugs and conquer the resistance of drugs in the patients. Among the bio-conjugates that are selected for enhanced curcumin bioavailability, the glutamoyl derivative has highest inhibition against the proliferative activities.

The better results in the case of curcumin bio-conjugates are probably due to their better solubility, enhanced cellular uptake through carrier proteins and decreased metabolic degradation. Though our work is still in its infancy, our results cannot be ignored. It opens a new era for exploring suitably designed curcumin bioconjugates as potential antibacterial, antifungal and antiproliferative drugs. Exhaustive work based on the designing and testing of the conjugates according to the molecular organization of several pathogens and cell lines is required before any definite conclusion can be reached. However, further studies are needed to evaluate the *in vivo* activity and selectivity of the compounds presented.

ACKNOWLEDGEMENT

The author is very grateful to those scholars whose articles are cited and included in the references of this paper and we acknowledge the authors, editors and publishers of all those articles, journals, and books from where the literature for this article has been reviewed and discussed. The author is also very thankful to Dept of chemistry, Pt DDU Govt. Girls PG College, Rajajipuram, Lucknow for the constant support during the research work.

Source of Funding: None

Conflict of Interest: No conflict of interest

Authors' Contribution: The work of this paper was done by Ramesh Baboo

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