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Review Article

New insights of structural activity relationship of curcumin and correlating their efficacy in anticancer studies with some other similar molecules

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Abstract: Recently, Cancer is the widespread category of different diseases in human beings, and its progress is linked with a number of factors such as estrogen level, diet, hereditary etc. Curcumin is a naturally occurring compound which appears to be significant clinical for applications *in vitro* as well as *in vivo* studies. Many of the research groups have been paying attention towards natural products for the development of anticancer drugs. Curcumin, Rosmarinic acid and Chalcone are the naturally occurring compounds, which are chemopreventive and chemotherapeutic. In present review the anticancer activity of curcumin and similar analogues *in vitro* has been discussed on the basis of inhibitory concentration (IC_{50}). Also this data is compared with the inhibitory concentration of chalcone, its derivatives and rosmarinic acid.

Keywords: Curcumin, rosmarinic acid, chalcone, anticancer activity

Introduction

Malignancy or carcinoma which is mainly due to stressful and unhealthy life style is becoming a big challenge for researchers. Uncontrolled growth of cells or tumors in different organs, blood cells (like WBC) or even in brain, is becoming unresolved challenges these days [1]. A chemotherapeutic study is becoming advanced for overcoming its side effects and improvements for the treatment of various types of cancers. 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, commonly called curcumin has potency to act as multifaceted anticancer agent [2-9]. Also, with minimum side effects, it is turning towards chemopreventive analog [1, 10] along with its chemotherapeutic nature [13-29]. With the presence of every substituent, its position and their structural activity relationship of curcumin help the researchers to generate better molecules.

Structural activity relationship

Looking at the basic structural framework of curcumin, it consists of symmetrically coupled substituted aromatic system with linker 1,3-dicarbonyl. Extensive data is available in the literature which shows the importance of each moiety and substitution in curcumin (**Figure 1**).

Interestingly, presence of two symmetrically coupled 1,3-dicarbonyl linker or α, β unsaturated carbonyl units helps in binding with DNA, protein sites and metals by undergoing a well-known process called keto-enol tautomerism [29]. Further, switching of keto form to enol form of curcumin is strongly dependent on the polarity of the system, making it suitable for crossing different barriers during biochemical processes. Another most important structural feature of curcumin is the hydrophobic aromatic unit with hydroxyl and methoxy substituents, which equally plays an important role in increasing efflux action of curcumin [29]. Due to the presence of two hydroxyl groups in curcumin it can also act as a strong antioxidant agent [11, 30-32]. As curcumin is used for the treatment of various diseases (as shown in **Figure 1**) but its anticancer studies have been explored to more extent.

Literature provides extensive data for preclinical and clinical studies which have supported

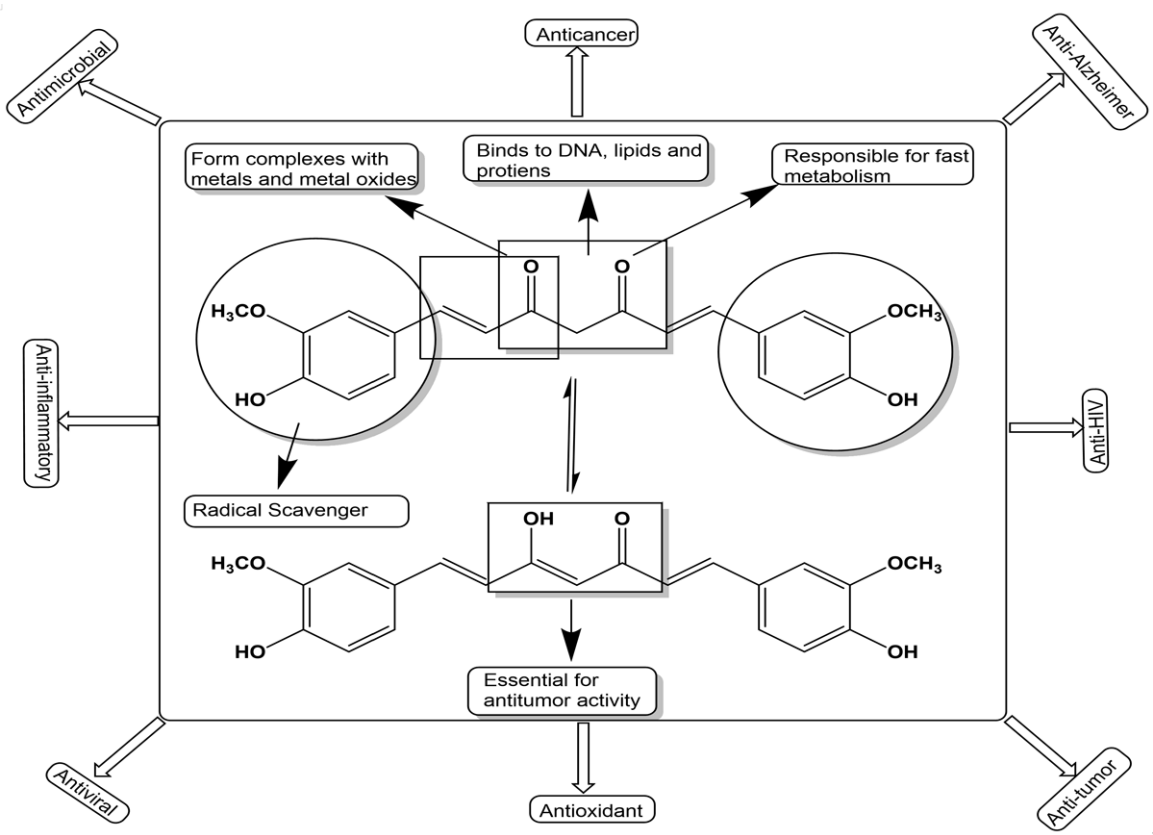

Figure 1. Structure of curcumin.

the efficacy of curcumin in both the prophylaxis and treatment of many tumors such as colorectal cancer, lung cancer, pancreatic cancer, breast cancer, multiple myeloma, melanoma, sarcoma etc. [33]. It has been summarized as various mechanisms for its molecular target in different type of cancers at their multiple phases such as it inhibits the stem like properties in breast cancer, NF-kb-regulate gene products in the DU-145 cells in prostate cancer and also reduces the size of tumor by suppressing special types of cellular signaling pathways both *in vitro* and *in vivo* studies [28]. It is also non-toxic compound with low bioavailability and lesser solubility property which limit its biological activities [2, 23, 25, 34-41]. To overcome this difficulty various research groups have introduced new derivatives with improved activity which has shown better results for particular activity as compared with multi-faceted activity of curcumin. Apart from the structural modifications of curcumin, several novel drugs delivery strategies such as liposomes, nano or microemulsions, polymeric NPs and solid lipid NPs, polymer conjugates, polymeric micelles, nanocrystals, nanogels, self-assemblies and cyclodextrin inclusion complexes have been described to increase the solubility, bioavailability and delivery of curcumin at the target [34]. Curcumin is proved to be wonder compound with hydrophilic as well as hydrophobic property making it suitable for penetrating various cell lines of different properties [42-44]. In this review article, comparative analysis of structural activity relationship and there *in vitro* anticancer studies have been described.

Anticancer activities of curcumin

During the process of carcinogenesis at multiple stages, curcumin is involved in several mechanisms including (a) the inhibition of tumor initiation (cytotoxic studies) (b) suppression of cellular proliferation (antiproliferation studies) (c) the induction of apoptosis (d) the inhibition of angionesis and metastasis (e) the inhibition of tumor induced immunosuppression [33]. Presently, a specified data regarding cytotoxic studies and antiproliferative results have been taken for comparison. **Table 1** repre-

Table 1. Anticancer and anti-proliferative activities of Curcumin

Anticancer Activity of Curcumin (μM)					Antiproliferative activity of Curcumin (μM)		
Cell line	Type	Method	IC_{50}	Reference	Cell lines	IC_{50}	Reference
Hela	Cervical cancer	MTT	27.4 22.25±0.29	[3, 45]	Hela	12.11±0.67	[52]
HepG2	Liver cancer	MTT	31.6 36.77±1.68	[3, 45]			
SkoV3	Ovarian cancer	MTT	37.7 43.63±0.63	[3, 8]			
A549	Adenocarcinomic human alveolar	MTT	42.6 60.2±2.6 18.93±2.1	[3, 8, 28, 46, 47]			
H1299			19.87±0.94				
H460			82.5±0.5				
A-431	Epidermoid carcinoma	MTT	13.8	[3]			
U-251	Glioblastoma	MTT & SB	13.8 59.1±4.9	[3, 23, 35, 45, 48]			
T98			54.8				
U87			62.9				
U87 MG			7.00±0.98				
U87 GBM			0.037				
MCF-7	Breast cancer	MTT	48.0 32.2±1.90 83.1±4.4 76.27 40.32	[3, 8, 28, 49, 50]	MCF-7 T47D MDA-MB-415 SK-BR-3	9.76 1.32±0.06 2.07±0.08 4.69±0.68 16.39±1.25	[53, 54]
MDA-MB-231			75.3±2.8 7.6 34.75		MDA-MB-231 MDA-MB-468 BT-20	11.32±2.13 18.61±3.12 16.23±2.16	
MDA-MB-468			1				
MDA-MB-435			37.48				
T47D			151.95				
PC-3	Prostate cancer	MTT	20.16±2.3 19.94±2.2 19.37±2.5 19.98±2.4 21.64±1.83	[28, 46, 47, 51, 52]	PC-3	25.43±2.15	[52]
RWEP-1			15.6±1.5				
DU145			41±2.9				
CWR-22Rv1			16.99				
LNCaP			3.8				
Panc-1	Human pancreatic cancer 56 years old male, Human pancreatic cancer	MTT	22.83±2.7 24.12±3.0 23.68±3.1	[28, 47, 51]			
BxPC-3			18.25±2.2 18.25±1.27				
HT-29	Human colon cancer	MTT	20.95±2.9 21.33±2.4 18.74±2.2 18.39±0.35	[28, 45-47, 51]			
HCT116			5.51±0.18				
AGS	Gastric cancer	MTT	9.77±0.77	[45]			
HCT-15	Colorectal adenocarcinoma	SB	13.9±0.6	[48]	HCT-15	13.9±0.6	[48]
K562	53 year old female chronic myelogenous	SB	59.9±5.0		K562	9.2±0.4	[48]

sents the cytotoxic results and anti-proliferative data which are evaluated using IC_{50} values from literature. The MTT assay has been taken for calculating these results. Analyzing the cytotoxic results, curcumin has shown its potency towards most of the cancer cell lines like Hela (Cervical cancer), HepG2 (Liver cancer), A549 (Adenocarcinoma human alveolar), MCF-7 and MDA-MB-231 (Breast cancer), PC-3, RWEP-1 and DU145 (Prostate cancer), SkoV3 (Ovarian cancer), A-431 (Epidermoid carcinoma), U-251, T98, U87, U87 MG and U87 GBM (Glioblastoma), Panc-1 and BxPC3 (Pancreatic cancer), HT-29 and HCT116 (Colon cancer), H1299 and H460

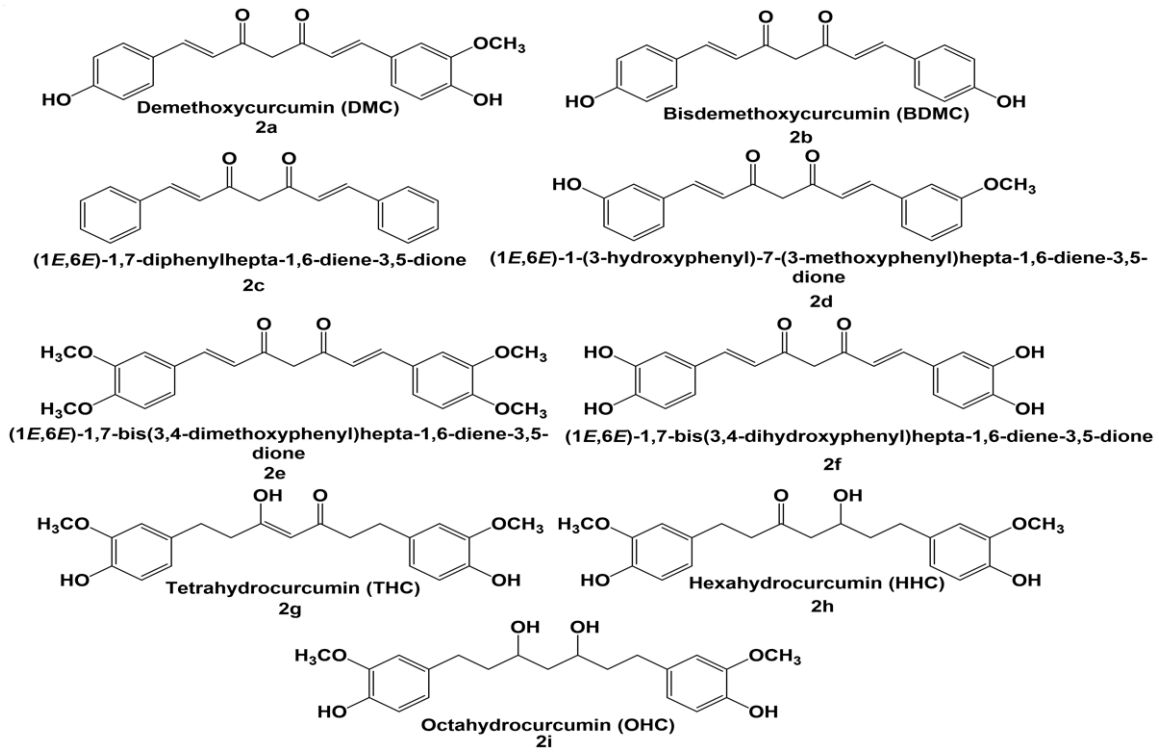

Figure 2. Structures of some derivatives of curcumin showing anticancer activity.

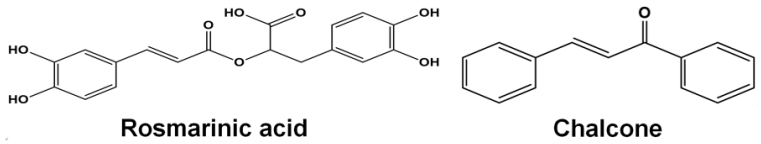

Figure 3. Naturally occurring compounds with similar symmetrical framework.

(Lung cancer), AGS (Gastric cancer), HCT-15 (Colorectal adenocarcinoma), K562 (Chronic myelogenous) etc. as shown in **Table 1**.

Epithelial tissues of various malignant organs have been taken in most of the *in vitro* anticancer studies, as cell lines. According to different studies, inhibitory concentration (IC_{50} values) represents the inhibition of cell growth and thus refers to cytotoxic nature which is further calculated using colorimetric method in MTT assay. At preliminary stages such inhibition of cell growth can be seen only if some interaction of molecule is possible. These interactions may be hydrogen bond donating affinity (due to the presence of hydroxyl group), hydrogen bond acceptor affinity (due to carbonyl group) and polar surface area (due to the presence of N, O and S) for binding with DNA or RNA of the cancer cell lines. Presently, two patterns of structural studies will be described in this article. First set of molecules include the compound with variations in their aromatic substitutions keeping the linker part unchanged as shown in **Figure 2**.

Anticancer activities of curcumin like compounds

In second set of molecules, the natural compound with similar symmetrical framework of the phenolic component but different linker has been selected such as Rosmarinic acid, Chalcone and their derivatives with variation in the number and position of hydroxyl and methoxy substitution as shown in **Figure 3**.

In **Figure 2** demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) are naturally occurring compounds, which shows enhance potency against cancer cell lines *in vitro* [20] and differ from curcumin in the position and number of hydroxyl and methoxy substitution pattern[21]. The presence of methoxy and hydroxyl group in curcumin plays a vital role in deciding

Table 2. Anticancer activity of curcumin like compounds

Cell lines	Type	IC_{50} (μM)				References
		DMC (2a)	BDMC (2b)	Dimc (2e)	THC (2g)	
MCF-7	Breast Cancer	17.73	0.23	23.62	> 50	[50, 57, 58]
MDA-MB-231				22.44		
PC-3	Prostate Cancer			1.1		[28]
CWR-22Rv1				< 1		
LNCaP		1.0	3.8	1.3		
Hela	Cervical Cancer				33.6±0.04	[57]
A-549	Lung Cancer				> 50	[57]
HepG2	Liver Cancer			1.1		[58]

Table 3. Anti-proliferative activity of Rosmarinic acid (RA) and Chalcone

Compounds	Cell Lines	Type	IC_{50} (μM)	References
			Anti-Proliferative activity	
RA	MCF-7	Breast cancer	381.75	[59, 60]
			> 300	
	HT-29	Colon cancer	526.30	[59, 60]
	SW620		95.63	
	DLD-1		96.05	
	HCT116		> 300	
	Hela	cervix epitheloid carcinoma	1261.05	[59, 60]
			> 300	
	A-549	human lung cancer	> 300	[60]
Chalcone	MCF-7	Breast Cancer	> 100	[62]
	MDA-MB-231		> 100	
	Hela	human cervical	> 100	[62]
	Caov-3	human ovarian cancer	> 100	[62]
	A549	human lung cancer	69.79±3.15	[62]
	HepG2	human liver cancer	> 100	[62]
	HT-29	human colorectal cancer	> 100	[62]
	CNE-1	human nasopharyngeal	> 100	[62]
	K562	human erythromyeloblastoidleukaemia	> 100	[62]
	CEM-SS	human T-lymphoblastoidleukaemia	> 100	[62]

various biological activities as reported by various research groups [31, 40]. Presence of phenolic group enhances its antioxidant activity by increasing its radical scavenging capacity [31, 38]. As shown above curcumin contains two different types of hydroxyl groups one of which is in the form of phenolic moiety and another in the form of enolic moiety [31, 39, 55, 56]. Enolic part of the molecule shows the better anticancer activities as indicated by the naturally occurring analogue suggesting the importance of enolic group along with that of the phenolic moiety. Presence of hydroxyl groups not only affect the antioxidant property, but also help in enhancing the hydrogen bond capacity of the molecule, and thus increasing hydrophilicity of the molecule. Such physicochemical properties may enhance the interaction of molecule with those cell lines which favors hydrophilic interactions.

It appears that more studies are required to correlate the hydrophilic properties of the molecules and their interaction with selected cell lines. It is also proposed to extend the study which highlights the selection of tissue culture during *in vitro* studies.

Table 4. Antiproliferative Activity of Chalcone Derivatives (Ref-62)

Compounds	MCF-7	MDA-MB-231	Hela	A-549	HepG2	HT-29	K-562
4a	47.16±1.56	16.22±2.98	32.26±0.48	24.04±0.53	47.72±1.93	45.25±5.92	39.39±1.45
4b	> 100	43.29±0.06	87.54±1.01	67.61±5.88	94.64±2.97	56.25±2.45	38.56±1.27
4c	> 100	41.89±0.50	> 100	61.68±0.36	> 100	> 100	36.01±1.01
4d	63.90±1.95	18.33±3.67	> 100	40.41±0.98	58.11±2.72	32.05±11.00	18.91±0.80
4e	12.00±1.96	20.22±3.08	> 100	20.97±0.14	18.52±3.91	17.98±5.04	23.65±1.12
4f	> 100	66.38±	> 100	76.87±4.92	> 100	> 100	> 100
4g	23.02±6.07	11.43±0.19	> 100	8.05±1.40	14.37±4.44	6.61±0.22	10.04±0.51
4h	7.53±0.71	36.68±0.66	17.91±0.43	5.52±0.11	4.56±0.21	4.54±0.20	4.68±0.29
4i	> 100	36.59±1.61	91.73±0.31	45.67±4.81	> 100	> 100	> 100

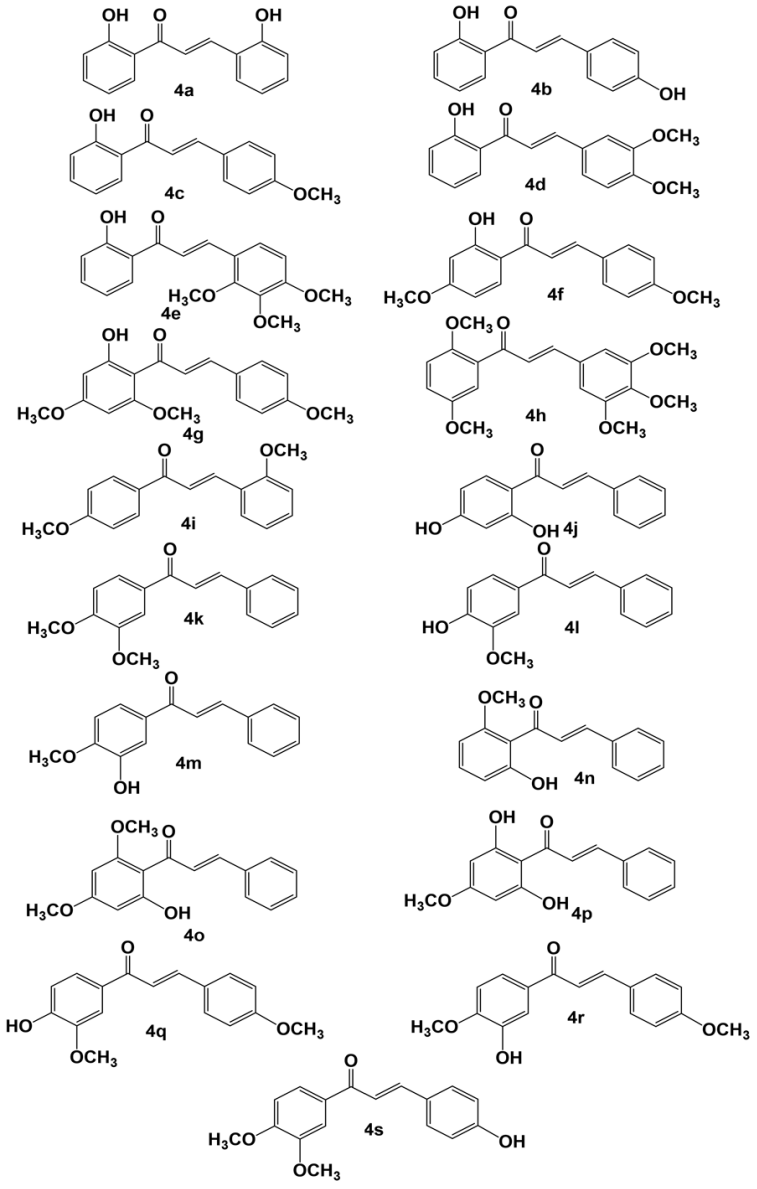

Figure 4. Chalcone.

As shown in **Table 2**, the Dimc which contains four methoxy substituents has shown its efficacy for breast cancer and prostate cancer.

As in the case of THC, HHC and OHC, only THC shows its potency as anticancer activity indicating that unsaturated system in the linker also plays a role in such studies. Since, sufficient anticancer activity with similar method of such compounds are missing in literature, a step has to be a taken to study the biochemistry of such cell lines, their interaction studies and their comparative data is required.

Anticancer activities of rosmarinic acid and chalcone

By replacing dicarbonyl linker of curcumin with ester linker (in Rosmarinic acid) or α, β-unsaturated linker (in Chalcone) has shown activity against cancer cell lines. Higher IC_{50} values for anti-proliferative data by TRAIL method of these compounds indicate the importance of dicarbonyl system of curcumin as shown in **Table 3** [59-62]. The data with unsubstituted chalcone shows less potency against cell lines and the IC_{50} value more than 100

Table 5. Cytotoxic analysis of Chalcone Derivatives (Ref-63, 64)

Compounds	MCF-7	A-549
4j	16.3	-
4k	37.8±0.20	25.8±1.50
4l	36.45±4.4	18.8±3.18
4m	45.7±0.50	25.05±0.75
4n	18.3	-
4o	20.0	-
4p	> 60	-
4q	74.0±0.5	28.1±4.1
4r	74.15±0.15	33.65±1.35
4s	40.74±0.26	28.83±0.88

μM. But with the introduction hydroxyl group and methoxy group the values are sharply decreased as shown in **Table 4** [62]. As chalcone does not consists of symmetrical linker moiety as in curcumin so the presence of different substituents, their positions, and their number and the ring of substitution is important during *in vitro* studies. Broadly, it is observed that presence of hydroxyl group at ortho positions of ring A and ring B (4a) of Chalcone shows greater potency against different cell lines.

*Discussion of various parameters of derivatives of chalcone (**Figure 4**)*

Variation in position parameter: Presence of hydroxyl group at ortho position on ring A and B (as shown in 4a) lead to increase in the potency against most of the cancer cell lines when compared with 4b, which differs in one of the positions of hydroxyl group on ring B.

Variation in substituent: With the introduction of methoxy group (4c) in place of hydroxyl group (4b) at para position on ring B, decrease in potency has been observed except A-549 cell line as shown in **Table 4**.

Effect of number of substituents: When the number of substituents have been increased, as in case of 4c < 4d = 4f < 4e = 4g, 4g has shown better results. But the role of position of substitution and presence of methoxy substituent on ring A or ring B also affect the IC_{50} values as in case of 4e and 4g where the position of methoxy group has been shuffled keeping the number of substituents same. The comparative results have shown that 4g is more potent than 4e excluding MCF-7.

Some compounds were analyzed which contain only methoxy substitution like 4h and 4i. It has seen that 4h has exceptionally shown superior results for anti-proliferative activity as shown in **Table 4**.

Another set of molecules has been discussed using cytotoxic results exclusively for two cell lines MCF-7 and A-549 as shown in **Table 5**.

4j contain only hydroxyl substitutions on ring A has shown enhanced potency against MCF-7 as compared to chalcone and 4k which contains only methoxy substituent on ring A.

It was seen that most of the available data consist of substitution towards ring A. So, by comparing the number and pattern of substitution the discussion was proposed. As seen in compound 4l, 4m and 4n containing one methoxy and one hydroxyl group on ring A, 4n has shown more activity against MCF-7 whereas 4l is active against both cell lines.

A comparative data for 4o and 4p have been seen which contains two methoxy substituents and one hydroxyl group (4o) is more potent than 4p.

Taking into account the substitutions towards ring B, three molecules i. e. 4q, 4r and 4s have been analyzed and it was seen that 4s is more active than 4q and 4r against MCF-7. Role of position has also been observed in molecule 4l and 4m which shows that 4l is more potent against both the cell lines than 4m.

All these analyses have proposed that the unsymmetrical pattern of linker in Chalcone has greatly influenced the activities. Still, a lot of analysis has to be worked out taking such parameters into consideration.

Studies of brain tumors are entirely different field of research than all other *in vitro* studies. Although the cell lines of brain tumor are epithelial type but as these tumors are surrounded by brain fluid which may not be suitable for hydrophilic interactions with various analogues. So, entry of blood brain barrier and central nervous system is big challenge for researchers to work on. Although *in vitro* studies of curcumin have shown increased potency for U-251 but similar results may differ *in vivo* studies. So, improving the solubility of curcumin is not only

the concept for increasing its efficacy against cancer but there are other parameters like lipophilicity, polar surface area which are equally important for such studies. According to physicochemical studies it has been observed that log *P* value of curcumin is high. So, it is more lipophilic in nature. This property further can be related to entry through central nervous system after crossing blood brain barrier [20, 65]. But after crossing BBB, hydrophilic nature of molecule may be required for the treatment against cancer cell lines. Therefore, solubility parameters in terms of lipophilic, hydrophilic, polar surface area etc. pivotal and prime point to start the anticancer study so that one can assume the availability of particular drug in CNS or peripheral system.

Conclusion

Pharmacological studies of curcumin and its similar analogues having common structural features attracted us to make a link between these parameters with the structural features. Understanding Chemistry alongwith different biochemical parameters and their comparison with other analogues is the main target of this review. Such combined studies involving various computational predictions, their preclinical studies and their analyses taking each structural parameter into consideration, are still unsolved for the emerging areas of drug discovery.

Disclosure of conflict of interest

None.

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