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Therapeutic and pharmacological potential of turmeric: An overview

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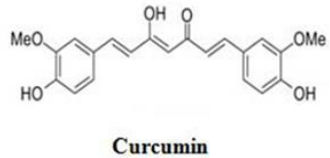
Abstract
Turmeric (*Curcuma longa*), is medicinal herb belongs to family Zingiberaceae. It is mostly useful as flavouring of foods throughout the World. It is extensively used in traditional and alternative medicine for the treatment and management of various ailments such as diabetes, allergies, arthritis, Alzheimer's and other age related chronic diseases. Many biological activities of turmeric have been reported such as anti-inflammatory, anti-oxidant, antimicrobial, neuroprotective, anti-muscles fibrosis, antiulcer, anticancer and hepatoprotective activities. The phytochemical studies of turmeric rhizome showed the presence of some flavonoids such as curcumin, demethoxycurcumin and bisdemethoxycurcumin and various volatile oils, including α turmerone, atlantone, and zingiberone. Turmeric also contains some other phytoconstituents include sugars, proteins, and resins. Curcumin is the main active constituents of turmeric and responsible for its therapeutics and biological activities. The purpose of this review is to provide the innovative knowledge of turmeric and its ingredients for treatment of various deadly diseases and a leading scope in the future research for researchers.

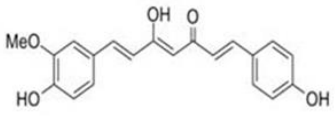
Keywords: turmeric, phytoconstituents, anticancer

1. Introduction
Turmeric (*Curcuma longa*), a perennial herb and member of the *Zingiberaceae* family, grows to a height of three to five feet and is cultivated extensively in Asia, India, China, and other countries with a tropical climate. Turmeric is used extensively in foods for its flavour and colour, as well as having a long tradition of use in the Chinese and Ayurvedic systems of medicine (Kumar *et al* 2011) [23]. The whole rhizome of turmeric appears as rough, segmented skin with yellowish-brown colour in outer and dull orange in interior. The primary active constituent of turmeric which is responsible for its vibrant yellow colour is curcumin; a major curcuminoids and other are demethoxycurcumin and bisdemethoxycurcumin. It also contains various volatile compounds such as turmerone, atlantone and zingiberone. These compounds were isolated through HPLC, GC-MS and TLC (Revathy *et al*., 2011) [40]. It is useful in the treatment of diabetics, hemorrhoids, anaemia, jaundice, cough, asthma, wound healing, colic, gout, renal calculi, poisoning, freckles, skin and neurological disorders. Many biological activities of turmeric has been reported such as antialzheimer, antidiabetics, anticancer, antineuroprotective, hepatoprotective, antimuscles, immunostimulant, antiseptic and antimutagenic (Nagpal and Sood 2013) [30]. Thus turmeric is a broad spectrum spice used against microbial infections along with oxidative damage.

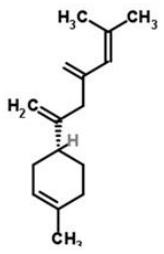
2. Phytochemicals and their biological activities
The main active constituent of turmeric is curcumin, which comprises 0.3–5.4% of raw turmeric (Akaram *et al*. 2010). Other compounds are curcuminoids demethoxycurcumin, and bisdemethoxycurcumin and various volatile oils including α turmerone, α and β atlantone (Figure 1).



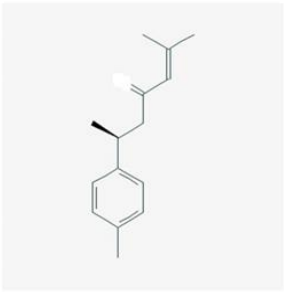
Curcumin



Demethoxycurcumin



Alantone


α turmerone

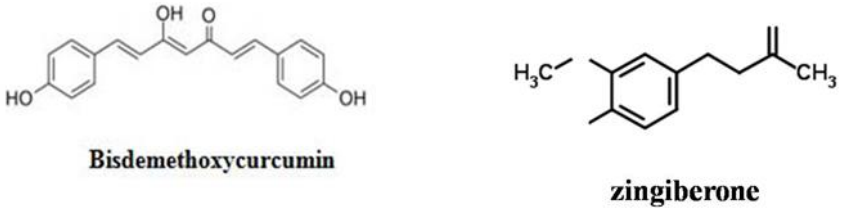


Fig 1: Bioactive constituents of turmeric

Curcumin

The principal compound Curcumin ($C_{21}H_{20}O_5$), also known as (diferuloyl methane or 1, 6-heptadiene-3, 5-dione-1, 7-bis (4-hydroxy-3-methoxyphenyl), was isolated in 1815 (Parthasarathy 2008) [37] and its chemical structure was determined in 1910 **(**Milobedzka *et al.* 1910) [28]. The compound is a yellow-orange powder with a molecular weight of 368.38 g/mol. It is water insoluble but can be dissolved well in ethanol, methanol, actone, and dimethysulfoxide (Li *et al*. 2011)

Biological activity of Curcumin

Antioxidant activity

Dietary and endogenous antioxidants prevent cellular damage by reacting with and eliminating oxidizing free radicals. The antioxidant activity of curcumin depends upon the presence of both the central methylene hydrogens and the phenolic hydrogens are involved in the mechanism of formation of the phenoxy radicals. So the curcumin effectively inhibit the free radical damage to biomolecules by prevention and intrusion processes which make it very unique natural antioxidant (Namratha *et al*. 2013) [31]. The antioxidant activity of curcumin was reported, as early as by Sharma *et al*. 1976. Curcumin acts as a scavenger of oxygen free radicals and can protect haemoglobin from oxidation (Unnikrishnan *et al*. 1995) [47]. *In vitro* curcumin can significantly inhibit the generation of reactive oxygen species (ROS) like superoxide anions ($O_2^{\bullet}$), hydrogen peroxide (H_2O_2) Hydroxyl radical ($OH^{\bullet}$) and nitrite radical generation by activated macrophages, which play an important role in inflammation (Joe *et al*. 1994) [18].

Anti-cancer activity

The general anti-carcinognic effect of curcumin involves the mechanisms like induction of apoptosis and inhibits cell-cycle progression, both of which are instrumental in preventing cancerous cell growth in rat aortic smooth muscle cells (Chen and Huang 1998) [9]. The antiproliferative effect is mediated partly through inhibition of protein tyrosine kinase and c-myc mRNA expression and the apoptotic effect may partly be mediated through inhibition of protein tyrosine kinase, protein kinase C, c-myc mRNA expression and Bcl-2 mRNA expression (Chen *et al*., 1998) [9]. Specifically, curcumin suppresses human breast carcinoma through multiple pathways. Its antiproliferative effect is estrogen dependent in ER (estrogen receptor)-positive MCF-7 cells and estrogen independent in ER-negative MDA-MB-231 cells (Shao *et al*. 2002) [43]. Curcumin also down regulates matrixmetalloproteinase (MMP)-2 and upregulates tissue inhibitor of metalloproteinase (TIMP)-1, these two common effector molecules involved in cell invasion (Shao *et al*. 2002) [43]. It also induces apoptosis through P^{53} dependent Bax induction in human breast cancer cells (Annapurna *et al*. 2011) (Figure 2).

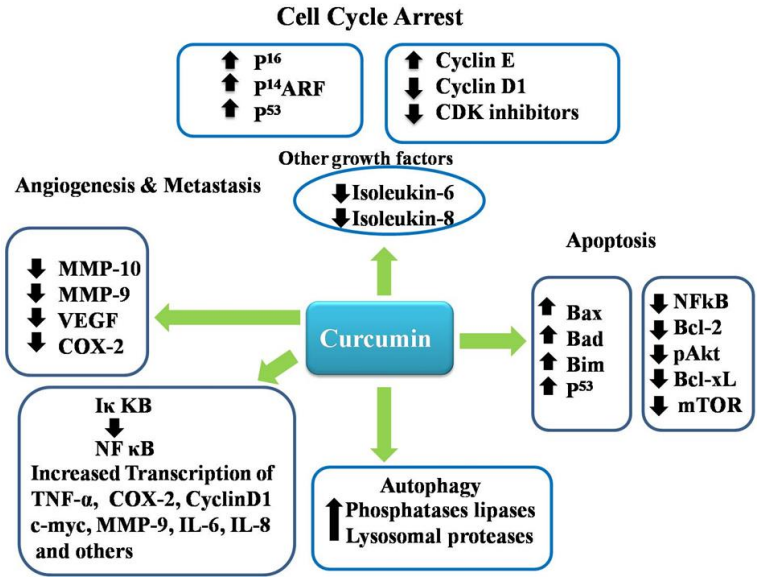


Fig 2: Anticancerous targets of curcumin

Curcumin efficiently induces apoptosis in various cells like HL-60, K562, MCF-7 and HeLa (Roy *et al*. 2002) [41]. Curcumin also leads to apoptosis in scleroderma lung fibroblasts (SLF) without affecting normal lung fibroblasts (NLF) (Tourkina *et al*. 2004) [46]. This effect seems to be due to the weak level of PKC (PK) C3 in SLF, generating low levels of glutathione S-transferase (GST). Studies of curcumin and ethanolic extract of turmeric *in vivo* (mice) and *in vitro* (human liver carcinoma cell line) have revealed that both curcumin and the crude ethanolic extract have reporting anticancer activity great potential in the prevention and cure of cancer (Naama *et al*. 2010; Ahmad *et al*. 2016) [29, 20]. Curcumin modulates several molecular targets and inhibits transcription factors (NF-kB, AP-1), enzymes (COX-1, COX-2, LOX), cytokines (TNF, IL-1, IL-6) and antiapoptotic genes (BCL2, BCL2L1) (Sandur *et al*. 2007; Bengmark *et al*. 2009) [42, 6]. As a Result, curcumin is able to induce apoptosis and has antiangiogenic activity (Li *et al*. 2011) (Figure 3).

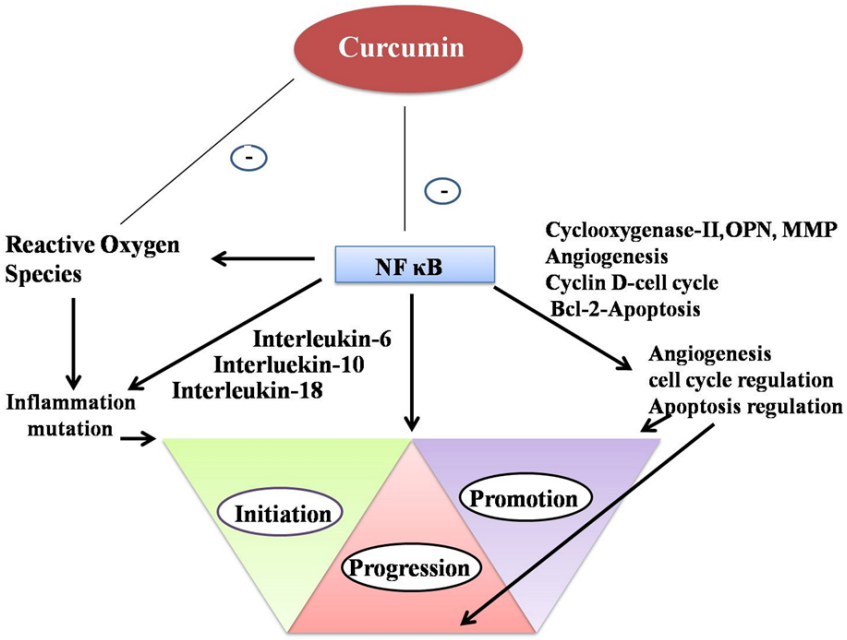


Fig 3: Antiangiogenic targets of curcumin

Anti-inflammatory activity

Anti-inflammatory activity of curcumin has been found to act at various different levels of the arachadonic acid, inflammatory cascade and through effects on various enzymes and cytokines. Based on the findings of the following studies, the anti-inflammatory effect of curcumin may be via the following different mechanisms (Chainani-wu *et al*. 2003) [7]. By decreasing the catalytic activities of phospholipase A2 and phospholipase C γ 1, thereby decreasing arachadonic acid release from cellular phosphoilipid (Rao *et al*. 1995) [38], Inhibitory effect on phospholipase D activity (Yamamoto *et al*. 1997) [49], Inhibition of cyclo-oxygenase-2 (COX-2) expression (Goel *et al*. 2001; Ramsewak *et al*. 2000; Zhang *et al*. 1999) [15, 51], Inhibition of lipopolysaccharide (LPS) and interferon-γ–induced production of nitric oxide in macrophages and nitrite in peritoneal cells (Chan *et al*. 1995) [8], Downregulation of chemokine expression monocyte chemoattractant protein-1 [MCP-1, and interferon-inducible protein) in bone marrow stromal cells (Xu *et al*. 1997) [48], Inhibition of incorporation of arachadonic acid into membrane lipids, inhibition of prostaglandin E2, leukotriene B4, leukotriene C4, inhibition of secretion of collagenase, elastase, hyaluronidase by macrophages (Joe and Lokesh 1997) [18].

Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase and inducible nitric oxide synthase (iNOS) enzymes; inhibits the production of the inflammatory cytokines tumor necrosis factor-alpha (TNF-a), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP), and migration inhibitory protein; and down regulates mitogen-activated and Janus kinases (Goel *et al*. 2008; Abe *et al*. 1999) [1]. Curcumin's inhibition of inflammatory cytokines is achieved through a number of mechanisms. *In vitro* studies indicate curcumin regulates activation of certain transcription factors such as activating protein-1 (AP-1) and NF-κB in stimulated monocytes and alveolar macrophages, thereby blocking expression of cytokine gene expression. Down-regulation of intercellular signaling proteins, such as PKC, may be another way in which curcumin inhibits cytokine production (Jurenka *et al*. 2009) [20].

Anti-bacterial activity

Helicobacter pylori is a Group 1 carcinogen and is associated with the development of gastric and colon cancer. A methanol extract of the dried powdered turmeric rhizome and curcumin were tested against *H. pylori* strains including. Both the methanol extract and curcumin inhibited the growth of all strains of *H. pylori* in vitro with a minimum inhibitory concentration range of 6.25-50 µg/ml (Mahady *et al*. 2002) [27].

Histological analysis clearly showed that curcumin is highly effective in repairing damaged tissue. All these observations

not only indicate the therapeutic potential of curcumin against *H. pylori* infections but also highlight the anti-inflammatory effect of curcumin. Various clinical trials suggest a therapeutic potential for curcumin in diseases such as familial adenomatous polyposis, inflammatory bowel disease, ulcerative colitis, colon cancer, pancreatic cancer, hypercholesteremia, atherosclerosis, pancreatitis, psoriasis, and arthritis (Goel *et al*. 2008). It has been claimed that curcumin and related compounds have anti-human immunodeficiency virus type 1 and 2 activity in a recent patent application (Pardee *et al*. 1994; De *et al*. 2009) [35].

Anti-Diabetic activity

Diabetic patients often suffer from fatty liver disease and other liver disorders (Babu and Srinivasan *et al*. 1995) [5]. Curcumin reduced liver weight and lipid peroxidation products in diabetic patients. In this study the beneficial effects of curcumin occurred independently of changes in glycemia or body weight. Babu and Srinivasan (1998) [4] suggested that hepatic cholesterol-7a-hydroxylase mediates the hypolipidemic action of curcumin in STZ diabetic rats. In sodium arsenite induced liver disorder rats oral administration of curcumin can decrease total lipid, cholesterol, triglyceride (TG), and low density lipoprotein-cholesterol (LDL-c) (Yousef *et al*. 2008).

AMP-activated protein kinase (AMPK) is a strong energy regulator that controls whole-body glucose homeostasis in the liver and other key tissues in type 2 diabetes (Deng *et al*. 2011) [12] AMPK could stimulate glucose uptake and mediate suppression of hepatic gluconeogenesis. G6Pase and PEPCK are key enzymes involved in hepatic gluconeogenesis in the liver. Increased expression of G6Pase and PEPCK may have deleterious effects in diet-induced insulin resistance and type 2 diabetes (Franckhauser *et al*. 2006). Kim *et al*. (2009) [22] Showed that curcumin inhibited PEPCK and G6Pase activities in H4IIE rat hepatoma and Hep3B human hepatoma cells. They further demonstrated that its downstream target acetyl-CoA carboxylase (ACC) (Shehzad *et al*. 2011) [44]. Currently, diabetic nephropathy is the leading cause of chronic kidney disease (Reutens *et al*. 2013) [39]. Curcumin decreases levels of albuminuria (Gutierres *et al* 2012) [16]. Curcumin can also restore renal integrity by normalizing glutathione, SODC, glucose-6-phosphate dehydrogenase, LDH, aldose reductase, SDH, transaminases, ATPases, and membrane PUFA/SFA ratio (Babu and Srinivasan 1998) [4]. A further study revealed that curcumin induces changes in posttranslational modification of histone H3 and altered expression of HSP-27 and p38 mitogen-activated protein kinase (MAPK) in diabetic kidneys (Tikoo *et al*. 2008) [45]. These changes were mediated through inhibition of p300 and NF-*κ*B (Chiu *et al*. 2009). Reported that curcumin activated the p38-MAPK-HSP25 pathway in mouse podocytes but failed to attenuate albuminuria in STZ-induced diabetes in DBA2J mice (Zhang *et al*. 2013).

Neuroprotective activity

Curcumin has been shown to exhibit activity against various neurological diseases, including Alzheimer's disease (AD), multiple sclerosis, Parkinson disease, epilepsy, cerebral injury, (Lim *et al*. 2001). The brain is a highly oxidative organ that consumes 20% of the body's oxygen despite accounting for only 2% of the total body weight. With normal aging, the brain accumulates metals ions such as iron (Fe), zinc (Zn), and copper (Cu). Patients with AD have defects in phagocytosis of amyloid beta by the macrophages and in clearance of amyloid beta plaques. Curcumin was found to enhance amyloid beta uptake by macrophages of patients with AD (Zhang *et al*. 2006). AD *in vitro* studies have demonstrated that curcumin and its analog, rosmarinic acid, have anti-amyloidogenic properties, dose-dependently inhibiting the formation and extension of neurotoxic Aβ fibrils from fresh Aβ, and destabilizing preformed Aβ fibrils to regenerate Aβ monomers (Ono *et al*. 2004). Inhibiting Aβ fibril formation represents an attractive therapeutic strategy for the treatment of AD; thus, given its primary effect on Aβ fibrilization, curcumin is a promising agent for use in treating and/or preventing AD (Ono *et al*. 2004) [32]. Curcumin inhibits the aggregation of α-synuclein, the protein involved in the pathogenesis of Parkinson's disease PD (Pandey *et al*. 2008) [34]. On the other hand, resveratrol may be useful in Huntington HD, as evidenced by its ability to protect cells against the toxicity of mutant huntingtin protein in HD experimental models (Parker *et al*. 2005; Kim *et al*. 2010) [36].

Anti-hepatoprotective activity

Cisplatin revealed a significant increase of hepatic malondialdehyde (MDA) levels and a significant reduction of hepatic superoxide dismutase (SOD) and catalase activities compared to the saline group. It elicited a marked increase of the serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and demonstrated the liver pathologies including liver congestion, disorganization of hepatic cords and ground glass appearance of hepatocytes. It also demonstrated a significant increase of NADPH oxidase gene expression compared to saline group. Pre-treatment with combined curcumin and α-tocopherol improved the liver enzymes, lipid peroxidation biomarker, liver histopathology and gene expression of liver NADPH oxidase in Cisplatin treated rats. Hepatoprotective effect of curcumin and alpha tocopherol against Cisplatin induced oxidative stress, indicate that pre-treatment with combined curcumin and α-tocopherol can protect cisplatin induced hepatotoxicity including the biochemical, histological and molecular aspects. The down regulations of NADPH oxidase gene expression may be involved in abrogating oxidative stress via reduction of reactive oxygen species (ROS) production (Palipoch *et al*. 2014).

The anti-digestive activity

Anti-digestive effect of curcumin exhibited many gastrointestinal diseases, both functional and organic. It appears to be a very promising therapeutic compound on the basis of thousands of preclinical studies, but its poor bioavailability has greatly hampered more widespread clinical use. However, the new formulation of curcumin with phospholipids has allowed us to overcome this problem by markedly improving intestinal absorption compared with the traditional unformulated curcuminoid mixtures. If curcumin is truly beneficial, as has been suggested by prior clinical trials using curcumin with limited bioavailability, we can expect to

see greater therapeutic effectiveness from phospholipid-complexed curcumin, which enables increased absorption and appropriate tissue delivery. These improved pharmacokinetic and pharmacodynamic properties are also able to significantly reduce the required dosages of curcumin and to increase the compliance of the product. Overall, these features make curcumin a very promising new therapeutic option for the treatment of gastrointestinal and hepatic diseases (Dulbecco and Savarino 2013) [13].

2. Demethoxycurcumin and Bisdemethoxycurcumin.

The Dimethoxycurcumin ($C_{23}H_{24}O_6$) [1, 7-bis (-4, 3-dimethoxyphenyl) 1, 6-heptadiene-3, 5-Dione] and Bisdemethoxycurcumin ($C_{19}H_{16}O_4$).1, 7-bis (4-hydroxyphenyl) hepta-1, 6-diene-3, 5-dione; Bis (4-hydroxycinnamoyl) methanea are synthetic curcumin analogue with higher metabolic stability over curcumim.

Biological activity of Demethoxycurcumin (DMC) and Bisdemethoxycurcumin (BDMC)

Anti-cancer activity

The molecular mechanism of anti-cancer activity of curcumin (C1), demethoxycurcumin (C2) and bisdemethoxycurcumin (C3) with Bcl-2 demonstrated that among the three curcuminoids, C2 binds more efficiently into its recognized active site. Human glioma U87 cells treated with curcuminoids resulted in activation of Bcl-2 mediated G2 checkpoint, which was associated with the induction of G2/M arrest and apoptosis. Luthra *et al*. (2009) showed that demethoxycurcumin induced Bcl-2 mediated G2/M arrest and apoptosis most effectively.

Phytochemistry of α Turmerone

The α Turmerone ($C_{15}H_{20}O$), 2-methyl-6 (4-methylphenyl) hept-2-en-4-one, a major compound separated from turmeric oil, promoted more effective anti-dermatophytic activity (Jankasem *et al*. 2013) [17].

Biological activity of α Turmerone

Anti-cancer activity

The curcuminoids curcumin, DMC, BDMC as well as α-turmerone, significantly inhibited proliferation of cancer cells in a dose-dependent manner. α-turmerone also induced a breast cell cancer line to undergo apoptosis, while both α-turmerone and aromatic-turmerone showed stimulatory effects on peripheral blood mononuclear cell (such as lymphocyte, monocyte or macrophage) proliferation and cytokine production. Yue *et al*. (2010) also showed the anti-proliferative effect of α-turmerone and immunomodulatory activities of aromatic-turmerone was shown for the first time. Alpha-turmerone also induced a breast cell cancer line to undergo apoptosis (Yue *et al*. 2010).

Anti-dermatophytotic activity

Arromatic-turmerone, a major compound in turmeric oil, showed effective antidermatophytic activity. It could be used as an active marker for quality assessment of turmeric oil and active ingredient in turmeric creams and other finished antifungal products (Jankasem *et al*. 2013) [17].

3. Atlantone

Atlantone ($C_{15}H_{22}O$). 1, 5-Heptadien-4-one, 6-methyl-2-[(1R)-4-methyl-3-cyclohexen-1-y-l].

Biological activity of Atlantone

Anti-tumour activity

For apoptosis or programmed cell death (PCD) active compounds were isolated from the hexanic extraction of the rhizome of *Curcuma longa*. With the several chromatographies, and spectral data, they were identified as arromatic-turmerone and β-atlantone. Exposure of human myeloid leukemia HL60 cells to clinically achievable concentrations of arromatic-turmerone or β-atlantone produced internucleosomal DNA fragmentation of approximately 200 base pair multiples and the morphological changes characteristic of cells undergoing apoptosis or PCD. This finding suggests that these agents may exert their antitumoral activity through induction of apoptosis (PCD) (Paek *et al*. 1996) [33].

Conclusion

Keeping in view the above mentioned biological properties of *Curcuma longa*, it is quite clear that turmeric being available in pure form, it would be easier to develop new drugs which can be more effective with less side effects. In recent years, it has been seen that there is a continuous enthusiasm in treating various diseases with natural products. Due to being nontoxic with a wide spectrum of biological functions, turmeric may find its application in the formation of various medicinal products which can help in the treatment of various diseases in coming future.

Conflict of Interest: None.

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