Sudarshan Publications

Available online at https://www.s-epub.in/

Pharma Research

An International Peer Reviewed, Indexed Journal

10.62655/s-epub.2022.v14.i02.pp1-38

CURCUMIN, A NATURAL GOLDEN DRUG AND ITS ANTICANCER ASPECTS FROM SYNTHESIS TO DELIVERY: A REVIEW

GEETA KRISHNAMURTHY[1], DEEPTI ROY[1], JYOTSNA KUMAR[1*]

Affiliation

[1]Department of Chemistry, MS Ramaiah University of Applied Sciences, Bangalore, India

Article info

Published on:26-12-2022

ISSN;0975-8216

Keywords:

Curcumin, *Curcuma longa*,

Drug delivery, Curcuminoids

Abstract

Cancer is a dreadful disease and, in most cases, leads to death even when it is being treated. Even though synthetic drugs are still in use for the treatment of cancer, the seriousness of the side effects of these drugs especially anticancer activity. Paper summarizes the chemistry and bio-metabolism of curcumin in the human body. Aim of this review article is to gather the dispersed efforts of researchers predominantly in improving the

bioavailability of curcumin. In the present review, comprehensive literature on anticancer activity of Curcumin via combination therapy, structure modification, synthesis of analogues, novel delivery systems have been highlighted. Besides, the review paper explicated several challenges associated with Curcumin as an adjuvant chemotherapeutic agent and emphasizes more on clinical studies.

INTRODUCTION

Worldwide, cancer has become the second most lethal disease. In 2018, it has been

reported that in the US alone, about 1.73 million new cases and more than 609,000 deaths occurred due to cancer [1]. Although there is a noticeable advancement in medical science and technology for cancer therapy, there is no decline in new cases and the rate of mortality in the same disease for the past few decades [2].

Normal body cells are governed by signalling pathways which give instructions according to the requirement and work in an orderly process. They divide when the body requires new cells while the old and damaged cells die on their own accord. In cancer, abnormal multiplication of cells happens [3].

Due to some triggering reaction inside or outside, the cells start dividing and re-dividing continuously even when the body does not require it. Also, the old cells do not die but survive and start dividing like the normal cells. These undifferentiated cells form a lump like structure called a tumour. Most cancers form solid tumours, but cancers of connective tissue are in the liquid state, for example, leukemia or blood cancer [3–6].

Mainly, tumours are of two types: Malignant and Benign. Benign tumours do not move out from their place of origin but grow to exert pressure on the surrounding body parts but do not invade other tissues or parts of the body. Such tumours can be removed by surgery and the patient becomes completely free from the disease as it does not recur. Malignant tumours, also known as cancerous cells, break open and invade the surrounding tissues. They can enter the bloodstream or the lymph and travel to other parts of the body, where it gets attached somewhere and starts dividing. This is called metastasis [6-7] (fig. 1).

Treatment for metastasized cancer becomes difficult as multiple treatments are required without the guaranty of complete cure, as there is always a possibility of recurrence [7]. In case of a normal healthy cell, it carries out all its functions in a programmed way, which is controlled by the genes which regulate the enzymes, hormones and proteins. All the signals sent by the genes reach the spot as per the requirement of cells. But cancerous cells can evade these signals and develop their system. A cancerous cell could develop its blood vessels parallel to the normal blood vessels of the body and use them for its growth [8, 9] (fig. 1).

Similarly, cancer cells can override the immune system, which under normal conditions protect the healthy normal cells, disrupt the other

functions of the cells or utilize the immune system for their benefit, thus saving themselves from destruction (fig. 1). So, if any change occurs in the genes, it gives rise to the malfunctioning of the body, leading to cause cancer. Thus, cancer can be termed as a genetic disease. Not all genetic changes cause cancer but genetic changes that bring about mutations of Deoxyribonucleic acid (DNA) may lead to cancer [3, 7, 9].

There are different types of cancer. Based on the place of origin, they can be grouped into 3 categories: (1) Carcinoma-cancer of epithelial cells (2) Sarcoma-cancer of connective tissue and (3) Leukemia or liquid tumour, which mainly arises from blood-forming cells and lymphomas that arise from cells of the immune system [10].

There are some characteristic features of cancer cells which help them to survive. These pro-survival traits of cancer cells have some unique features, such as cancer cell, when divide, they never differentiate as normal cell; cancer cells lack normal signalling responses, nuclei of cancer cells are abnormal and larger than the normal cell which is also asymmetric. They also have changes in the chromatin, abnormalities to structures called mitotic spindle that assist in cell division and various genetic abnormalities like a mutation in gene sequencing. Cancer cells utilize glucose 5 or 10 times more than the normal cells for their energy instead of oxygen production. They can also be called as “metabolite parasite” because they steal energy from the host. Mitochondria with mutated genes as well as the changed protein structures and enzymes, are present in the cancer cell. Cancer cells can form new blood vessels which help in delivering oxygen and nutrients to the cancer cell. This is done by sending out chemical signals that promote angiogenesis [10].

Thus, for the prevention and treatment of this deadly disease, understanding of molecular alterations and progression are the key factor. Treatment for this disease depends on the type of cancer, stage of the disease and the age of the body. Many treatments are available to treat the disease but the commonly used (conventional methods) are surgery, radiation therapy and chemotherapy. If cancer has not metastasized, then removal of the infected tumour is done by surgery and patients can be completely cured [11]. Radiation therapy is mostly used in combination with other therapies where high energy gamma rays or X-rays are made to fall on the cancerous part, which shrinks or destroys the cancer cells. It makes the patient completely free from the disease and increases the survival rate [12]. Chemotherapy is a mode of introducing chemicals (drugs) into the body to kill the cancerous cells. Drugs

may be synthetic, semi-synthetic or natural. This mode of therapy can be advised at all stages of the disease, but this is specifically advised when the cancer cells have metastasized as these chemicals can travel throughout the body [13, 14]. Both radiation therapy and chemotherapy have serious side effects. Radiation damages the healthy cells surrounding the cancerous tissue, which may or may not recover at all. Chemotherapeutic drugs can also cause nausea, hair fall, fatigue, and vomiting [12–14]. Thus, considering noxious side effects, deadly off-target effects and ineffective expressions are prevalent phenomena for most of the current therapeutic protocols. Recently with the advancement of technology, various modern techniques have been developed like immunotherapy, hormone therapy, gene therapy etc. In immunotherapy, chemicals are introduced, which triggers the immune system of the body and the body becomes self-sufficient to fight the disease and restore normalcy. In the body to local immunotherapy, only the affected area will be administered by agents, while systemic immunotherapy treats the whole body [15, 16]. Immunotherapy can be considered targeted if the treatment specifically tells the immune system to destroy the cancer cells and it can be considered non-specific if it improves the cancer-fighting abilities by stimulating the immune system. Several types of cancer are linked to some types of hormones, such as in breast (oestrogen) and prostate cancer (testosterone). Hormone therapy is designed to change the hormone production in the body to stop the growth of cancer cells or to kill them completely. Cell activities are governed by hormones secreted by the cell itself. Similarly, the cancerous cell also secretes hormones which help in the proliferation of the cells. So, if the secretions of these hormones are altered, they can bring about cell death. For example, Tamoxifen drug, given to breast cancer patients, helps in reducing the production of oestrogen hormone, thereby inducing cell death. Similarly, prostate cancer can be treated by reducing testosterone hormone levels [17].

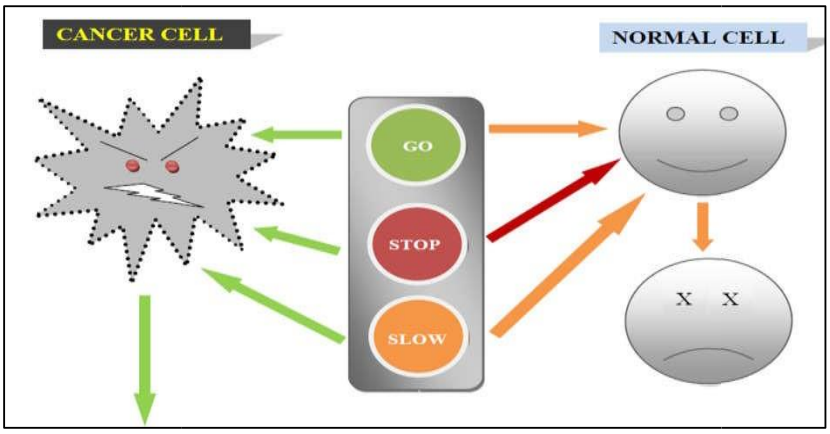


Fig. 1: Six hallmarks of cancer [3]

The goal of gene therapy is to replace the damaged genes with the new one that works to address the cause of cancer. Gene-based therapies also focus on further damaging cancer cell DNA to the point where the cell commits suicide. If genes responsible for cancer are altered or replaced in DNA, the cells start functioning normally [18–2].

These modern therapies are still in the nascent stage yet to receive success. Researchers are trying to find out alternative drugs/treatments, which will be more efficient, cost-effective with less or no side effects and helpful in increasing the survival rate. Researchers adopted many strategies by targeting explicit cancer cells, to impede or to control the growth, progress and metastasis of tumors without causing severe side effects [22]. used individually, was

One such process used for the treatment is a combination of drugs which are being used in monotherapy. Different combination of drugs was being experimented to overcome the resistance for the single drug by cancer cells or for the synergistic effect of the drugs or to enhance the effect of the main drug towards the disease. In this method, two or more drugs were used in combination to find their synergistic effect in arresting proliferation or apoptosis of cancer cells.

Combination of Dabrafenib and Trametinib, which were used as proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B (BRAF) inhibitor and MEK [acronym MEK derives from Mitogen-activated protein kinase/extracellular-signal-regulated kinase (MAPK/ERK Kinase in ibitor)] when

tested to find out whether it could delay the resistance of the drugs in the treatment of metastatic melanoma. The experiments showed a delay in resistance, which improved the survival rate of patients with metastatic melanoma due to mutation of BRAF V600E or V600K [23]. Authors concluded that this combination is successful, provided the side effects are properly addressed [23, 24].

Laboratory synthesized small molecule drugs in combination with anticancer drugs were tested for its efficacy and efficiency on the treatment of breast cancer using Michigan Cancer Foundation-7 (MCF-7) cell lines. Anticancer drugs, 5-Fluorouracil (5-FU), Oxaliplatin and Taxol was used in combination with two synthetic α-methylene-δ-lactones with chroman-2-one skeleton and compared with Parthenolide, a plant-derived α-methylene-γ-lactone, which was considered as the positive control. The results showed that the combination of α-methylene-δ-lactones with chroman-2-one skeleton with 5-FU and Oxaliplatin showed a synergistic effect in MCF cells [25]. Various other combination of drugs was tried, like a combination of Trastuzumab, Paclitaxel, Carboplatin and their results were compared with the combination of Trastuzumab and Paclitaxel to treat women having a protein called human epidermal growth factor receptor 2 (HER-2) overexpressing Metastatic Breast Cancer. The response was good, and survival increased with the introduction of Carboplatin to the combined drugs Paclitaxel and Trastuzumab [26].

Administering drugs orally or intravenous faced some drawbacks such as the drug may not reach the target site or even if it reaches dose may not be sufficient. Metabolism or loss of some amount is possible before reaching the target site. Thus, to make the drug more effective scientist explored many drug delivery tools in the form of nanoparticles, hydrogel system, nanotubes, metal complex, coordination polymer etc.

Nano coordination polymer particles loaded with Oxaliplatin and Gemcitabine were used to find the synergistic effect on Human pancreas adenocarcinoma cell line (AsPc-1) and human pancreatic cancer cell line (BxPc-3) cancer cell lines. Results revealed that the therapeutic effects of drugs increase many folds rather than when drugs were given individually or in combination without using any delivery system [27].

Gemcitabine and Cis-platinum were co-delivered using a biodegradable thermosensitive hydrogel system in the treatment of pancreatic cancer. Authors noted a strong synergistic effect of the drugs on the pancreatic cancer cell line Bxpc-3 with reduced side effects [28].

In a review paper, authors mentioned different combination strategies like chemotherapeutic combination, nucleic acid-based co-delivery, intrinsic sensitive and extrinsic stimulus combinational patterns, and combination therapy involving nanomaterials as drug delivery system. They concluded that nanomedicine-based combination anticancer therapy could be employed for the synergistic activity in cancer treatment, which synergistically improved anti-cancer outcomes. There are certain challenges to be faced in the combination therapy of nucleic acids and small drug molecules like drug resistance by the cancer cells, the difference in the pathways of the drug action, ratio of the drug combination etc. [29, 30].

All the above-mentioned methods of drug delivery have some drawbacks like multidrug resistance, differences in modes of action of drugs etc. So, progress in research led the researchers to turn towards natural products as they have been used as home remedies
i.e. first aid treatments for various diseases. This has opened the doors for products found in nature to be used as drugs for the treatment [31].

Many natural products are being used as traditional medicines in branches of medicine like Ayurveda, Unani, Homeopathy [32-34] etc. Natural products are finding prime importance along with allopathic medications

for their easy availability, lesser side effects, and synergistic effects. Plants and herbs have been used traditionally since ancient times as home remedies for simple ailments like the common cold, diarrhoea, inflammation, small burns, or cuts etc. [35]. They are rich in bio-components, responsible for the special activity like antioxidant, anti-inflammatory, antibacterial, antimalarial, antimutagenic, anticancer etc. A lot of research work has been carried out on secondary metabolites of plant and herbs like polyphenols, flavonoids, terpenoids, saponins and brassinosteroids. Scholars explored their effects and efficiency for several therapeutic values. Phyto components have shown very promising results with less toxicity [31, 35]. Many secondary metabolites of plants have been identified and studied for their anti-cancer activity, antioxidant activity, inhibition of cancer cell growth, induction of apoptosis, target specificity, cancer cell cytotoxicity etc. [35].

Silver nanoparticles prepared using *Bauhinia variegata* have shown antibacterial activity against some strains of bacteria like *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* [36]. Silver nanoparticles prepared from the bark of *Ficus krishnae* have been tested for antibacterial and anticancer activity which have a great affiance against them [37]. Gymnemic acid extracted from *Gymnema sylvester* has shown interesting biological profile with low cyto-permeability [38].

By green synthesis approach, the synthesis of silver nanoparticles was carried out by using leaf extract of *Psidium guajava*. Prepared silver nanoparticles were encapsulated with a biopolymer i.e. dextran sulphate as a stabilizing agent. Cytotoxicity of the prepared silver nanoparticles was investigated against MCF-7 cell line. By exhibiting 91% of cell inhibition, prepared dextran sulphate stabilized green silver nanoparticles have shown potent anticancer activity against MCF-7 cell line [39].

Extracts from turmeric, ginger and garlic were studied for their activity against breast cancer cell lines MCF-7, Human Caucasian breast carcinoma (ZR-75) and M. D. Anderson-Metastasis Breast cancer-231 (MDA-MB 231). Authors noted that plant extract had radical scavenging property and led to apoptosis in all the cell lines namely MCF-7, ZR-75, and MDA-MB 231 [40]. Numerous anticancer combinations with different approaches have been utilized from herbs and plants sources, such as *Catharanthus roseus*, *Taxus brevifolia*, *Betula alba*, *Erythroxylum pervillei*, *Cephalotaxus* species, *Curcuma longa* and

many others [41].

To amass the depth information on *Curcuma longa*, literature survey (1964-2020) was done from peer-reviewed research articles from globally reputed journals such as Science Direct, Mendeley, Royal Society of Chemistry, Springer link, PubMed Central (PMC), Multidisciplinary Digital Publishing Institute (MDPI), search libraries of World Health Organization (WHO), National Library of Medicine (NLM), Council for Scientist and Industrial Research (CSIR), Shodhganga, etc. Used keywords were mainly curcumin, anticancer activity, drug delivery, nanoparticles, and bioavailability. To write this article, predominantly used search criteria was the combination/formulation of curcumin to enhance its anticancer activity. From years as traditional medicine, different curcuma species are well documented for several therapeutic activities. In the present review article, to understand the action mechanism of Curcumin, its chemistry, degradation and metabolism have been summarised. Furthermore, to increase the bioavailability of curcumin, this review article discussed the several strategies and emerging technologies opted by scholars.

Of all the medicinal plants, Curcumin, an important phytochemical of herb *Curcuma longa* of the ginger family, has been of great interest. In 1870, Curcumin was extracted from *Curcuma longa* (turmeric plant) for the first time in the crystalline state [42, 43]. Multi bio- functionality properties of Curcumin and its derivatives have received enormous attention by the researchers such as anti- bacterial, antimalarial, antimutagenic, anti-tumor, antioxidant, anti- inflammatory activities etc. [44]. Most of the properties are endorsed due to the presence of key elements in the chemical structure of Curcumin [45].

Thus, a lot of scientific work has been done on Curcumin and its derivatives. To improve the biological and physicochemical properties of Curcumin, numerous research work shed light on the Structure-activity relationship (SAR) of different key functional groups present in Curcumin. In quest of treating cancer with more efficacy by using anticancer agents of less toxicity and fewer side effects, this review has primarily engrossed on the Curcumin and its anticancer activity. Authors reported that Curcumin is capable to

suppress numerous cellular signalling pathways which supports its anticancer activity [46]. Curcumin is capable to target several cancer cell lines including breast cancer cell lines, lung cancer cell lines, prostate cancer cell lines, brain tumours and head and neck squamous cell carcinoma [47].

Although Curcumin, a golden spice, exhibited multidimensional therapeutic advantages, it has certain limitations which hinder its broad-spectrum applications like poor water solubility, stumpy chemical stability, low oral bioavailability, and less cellular uptake [48, 49]. Hydrophobic nature of Curcumin makes its molecule to breach into the cell membrane and bind up with fatty acyl chains of cell membrane lipids via hydrophobic interactions and hydrogen bonding. This causes less accessibility of Curcumin in the cytoplasm. Hence, to overcome all these issues and to make Curcumin more effective and selective towards cancer cells, several strategies are suggested and explored by the researchers. Among them, structural modifications in Curcumin, synthesis of Curcumin analogues, use of Curcumin in combination therapy, different delivery systems for delivery of Curcumin alone or with other drugs etc. are few approaches. The present review focuses on recent literature on the chemistry of Curcumin, Curcumin in combination therapy and novel ways of delivery systems that have been experimented by authors for cancer therapy.

Curcuma species

Curcuma species are herbaceous plants with thick, fleshy rhizomes, pseudo stems and leaf blades have flower spikes that arise from the top of the pseudostem or sometimes on a separate stem directly from the rhizome. The inner part of rhizomes come in different colours, like white, cream, yellow, orange, blue, bluish-green, and black [50].

Rhizomes of this plant are widely used as flavouring preservative and colouring agent. The main bioactive constituent extracted from this rhizome is Curcumin, which is responsible for the therapeutic property of turmeric. A wide range of *Curcuma* species had been explored for different activities in several extracts obtained from different solvents, which are listed in table 1.

Table 1: Curcuma species and their activities

Name of species	Solvent extract	Bioactivity	Reference
Curcuma aeruginosa	Aqueous extract	Antioxidant, Anti-inflammation	[51] Wan-Ibrahim *et al.*, [52] Angel *et al.*
Curcuma amanda	Aqueous extract	Antioxidant, Anti-inflammatory	[53] Venugopalan *et al.*, [52] Angel *et al.*
Curcuma aromatia	Aqueous extract	Antioxidant, Anti-inflammatory	[54] Lee *et al.*, [52] Angel *et al.*
Curcuma brog	Aqueous extract.	Anti-inflammation	[52] Angel *et al.*
Curcuma caesia	Aqueous extract, Enzymic and crude extract	Anti-inflammation, Antioxidant	[52] Angel *et al.*, [55] Dhal *et al.*
Curcuma comosa	Aqueous extract	Antioxidant	[56] Boonmee *et al.*
Curucma domestica and Jantan	Aqueous extract	Antioxidant	[57] Saputri
Curcuma haritha	Aqueous extract	Antioxidant	[58] Rajan *et al.*

Curcuma kwangsiensis		Essential oils	Antifungal	[59] Zhang *et al.*
Curcuma longa	Aqueous extract, Benzene extract, Ethyl alcohol OH extract, Essential oils	Antioxidant, Anti-inflammatory, Hypoglycemic, Antimutagenic, Anti-atherosclerosis, Hypolipidemic, Cardiovascular protective, Insecticidal, Anti-oxidant, Anti-proliferation	[60] Vankar, [61] Manda *et al.*, [62] Dinesha *et al.*, [63] Ramadas and Srinivas, [64] Chandrasekaran *et al.*, [65] Madan *et al.*, [66] Mohankumar and McFarlane, [67] Azuine *et al.*, [68] Jin *et al.*, [69] Zhang *et al.*, [70] Rafatullah *et al.*, [71] Chander H, [72] Prakash *et al.*, [73] Idris *et al.*, [74] Jacob and Toloue, *[75]* Yan *et al.*	
Curcuma malabarica		Aqueous extract	Anti-inflammation	[52] Angel *et al.*
Curcuma manga	Aqueous extract, Methyl alcohol extract	Antioxidant	[51] Wan-Ibrahim *et al.*, *[76]* Chan *et al.*	
Curcuma mutabilis		Aqueous extract	Anti-oxidant	[58] Rajan *et al.*
Curcuma neilgherrensis		Aqueous extract	Anti-oxidant	[58] Rajan *et al.*
Curcuma ochrorhiza		Hexane extract.	Cytotoxicity	[77] Sukari *et al.*
Curcuma phaeocaulis		Ethyl alcohol extract	Antifungal	[78] Li *et al.*
Curcuma rakthakanta		Aqueous extract	Anti-inflammation	[52] Angel *et al.*
Curcuma sylvatica		Aqueous extract	Anti-inflammation	[52] Angel *et al.*
Curcuma vamana	Aqueous extract	Antioxidant	[58] Rajan *et al.*	
Curcuma viridiflora		Methyl alcohol extract	Antioxidant	[79] Chen *et al.*
Curcuma wenyujin		Ethyl alcohol extract	Antioxidant	[80] Lou *et al.*
Curcuma xanthorrhiza	Aqueous extract, Methyl alcohol extract	Anti-oxidant	[81] Qader *et al.*, [57] Saputri and Jantan	
Curcuma zedoaria	Aqueous extract, Methyl alcohol extract	Anti-inflammation Anti-oxidant	[82] Ullah *et al.*, [83] Hong *et al.*, [79] Chen *et al.*	
Radix curcumae	The plant	Gastric protective	[84] Lu *et al.*	

In another review, Arnab Sen presented the anticancer activity of some curcuma species, which is listed in table 2 [85].

Table 2: Anti-cancer activities of different curcuma species

Name of species	Name of tested cell line	Conclusion	Reference/s
Curcuma Amanda Roxb. (Common name-mango ginger)	Anti-cancer activity on lung cancer cell line H460 of the 60 cells lines from National Cancer Institute (NCIH460) and adenoca DNA rcinomic human alveolar basal epithelial cells (A-549) is	Herb acts through AKT (AK mice strain Transforming capabilities) also known as Protein kinase B (PKB) signalling pathway	[86] Policegoudra RS *et al.*, [87] Gonzalzez MA *et al.* [88] Bing H *et al.*, [89] Li Y *et al.*
Curcuma aromatica (Common name-wild turmeric)	reported to be due to the presence of compounds like difurocumenonol and amadaldehyde Sesquiterpenoids β-element, Germacrone and Curcumin derivatives are present in *Curcuma aromatica* which showed Inhibition of human colon carcinoma cell (LS-174-T) anti-proliferation was observed.	It involves in induction of apoptosis via down regulation of cyclin B1 and Cyclin-dependent kinase 1 (CDK1) and without the participation of p53. *C. aromatica* oil was also found to exhibit antiproliferative effect on human hepatocellular carcinoma Hepa1-6 cells	[90] Shaikh A M *et al.* [91] Mohammad P *et al.*
Curcuma caesia (Common name– Black turmeric)	Antitumor activity of this herb was tested on three human-cancer cell lines-(MCF-7) human breast cancer, human colon cancer cell line (HCT-116) and ovarian Cancer cell line.	Anti-cancer activity was shown to be active through the tumour necrosis factor alpha (TNF α) mediated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathway	
Curcuma longa Common name-Turmeric)	*Curcuma longa* have shown anti- tumour effect on human colon carcinoma cells lines (HCT116, SW480, CaCo2, HT29, and SW837). n-Hexane extract is more effective on human lung cancer cell line (A549). Curcuma C20-di-aldehyde which was isolated from this rhizome was able to supress the proliferation of HCT116, HT29 and Henrietta Lacks (HeLa cells).	Curcuma longa shows inhibition of telomerase activity in a dose-dependent manner	
Curcuma mangga	Herb has been reported to	i	n

	hibit tumour growth in (MCF-7), Human Colorectal Adenocarcinoma (HT-29), prostate cancer (PC-3) cell lines	*Curcuma mangga* induces early and late apoptosis and arrested the cells at the G0/G1 phase.	[92] Karsono AH *et al.*
Curcuma purpurascens (Common name– Temu Tis)	This herb induces apoptosis in (HT-29) human Colorectal denocarcinoma cells. Different extracts have shown different activity.	Induction is through activating the mitochondrial death pathway via the Protein family/associated X protein/B-cell lymphoma -extra large (Bcl-2/Bax/Bcl-xl) and reactive oxygen species (ROS) production.	[93] Rouholla hi E *et al.*, [94] Hong S *et al.*
Curcuma xanthorrhiza (Common name– Temu Lawak)	Antiproliferative activities were found by this herb on MDA-MB-231, MDA-MB-453, Memorial Sloan–Kettering Cancer Center (SK-BR-3), MCF-7, YMB-1 and T47D different breast cancer cell lines	Inhibitory effect may also be due to augmentation of COX-2 expression levels by other constituents of the rhizome Antitumor effect was due to Bisabolane Sesquiterpenoids, α-Curcumin, ar-turmerone and Xanthorrhizol.	[95] Oon SF *et al.* [96] Seo W *et al.*, [97]Pal P *et al.*
Curcuma zedoaria (Common name -white turmeric)	This herb shows specificity towards human oesophageal cancer cells (TE-8).	It induces apoptosis through caspase cascade dependent pathways, which involved activation of caspase-9, caspase-3 and Poly (ADP-ribose) polymerases (PARP) along with suppression of Bcl-2 through the intracellular signaling pathway (Akt/mTOR).	

Study of the above tables indicates that of all the given species of *Curcuma*, *Curcuma longa* shows a broad spectrum of therapeutics as well as anti-cancer activity on several cell lines.

Curcuma longa Linnaeus (common name- turmeric) belongs to Plantae kingdom of Magnoliophyta division in zingiberaceous order (Family: Zingiberaceae, genus: *Curcuma* and species: *longa*) [98]. *Curcuma longa* is used as a medicine for nearly 4000 y. *Curcuma longa* is a principal spice in Asian kitchens in the form of a yellow powder colouring agent [99]. The rhizome of *Curcuma*

-

longa is rich in several bioactive components (fig. 2). Curcumin is the main bioactive component of *Curcuma longa*. A wide range of therapeutic properties of *Curcuma longa* is mainly due to Curcumin from cough-cold to cancer treatment [100]. Curcumin, a polyphenol, is seeking the attention of researchers, especially in the field of pharmacy, medicine and in chemistry.

It has also been seen that Curcumin can modulate many molecular targets, which are the causes for the onset of many diseases in the human body (fig. 3) [101].

Fig. 2: Flowers and rhizomes of curcuma longa

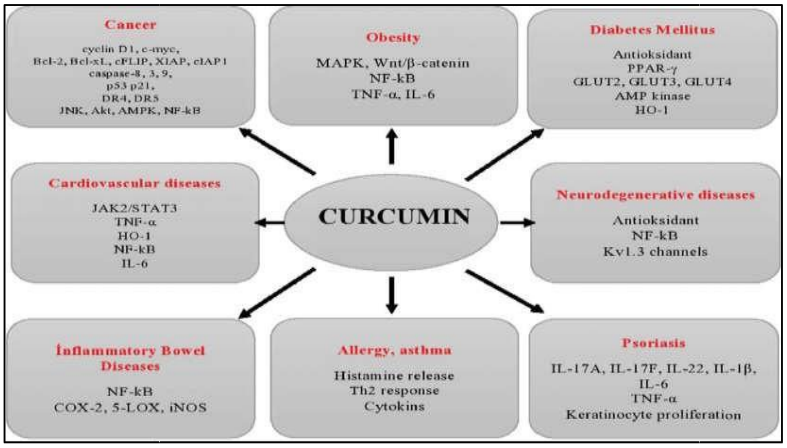


Fig. 3: Molecular targets of curcumin [101]

Chemistry of curcumin

Curcumin is known as diferuloylmethane and its chemical formula is C21H20O6 with molecular weight 368.38. IUPAC name of Curcumin is 1, 7-bis (4-hydroxy-3-methoxyphenyl) hepta-1, 6-diene-3, 5-diene. In Curcumin, three chemical entities-and α, β-unsa diketone moiety and two aromatic rings with o-methoxy phenolic groups are present. Both aromatic ring with o-methoxy phenolic groups are connected via α, β-unsaturated β-diketone moiety i.e. a linker with 7 carbon atoms [102-104].

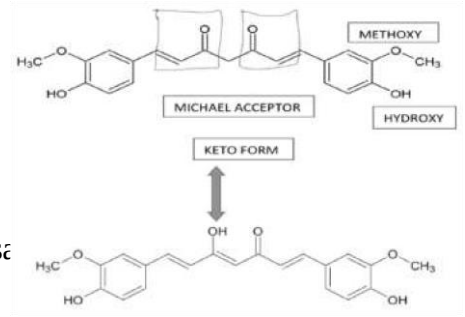
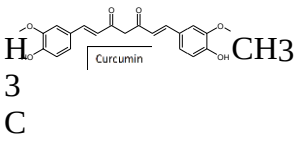
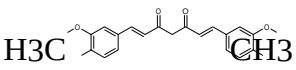


Fig. 4(b): Keto-enol forms of curcumin [103]

Diketo group of the Curcumin exhibited keto-enol tautomerism. Depending on the environment, keto-enol tautomerism (fig. 4a and 4b) can exist in different conformers. In non-polar and in moderately polar solvents, enol form is more stable than keto form. In crystal state, Curcumin stays in cis-enol configuration. In solution, Curcumin exists as cis-trans isomers where transform (when both phenolic-
methoxy groups are on the opposite sides) is s omewhat more stable

than the cis-form (where both phenolic-methoxy groups are on the same sides on the backbone of Curcumin) [103, 104].





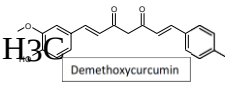


Fig. 4 (a): Structure of curcumin

Depending on the geological conditions where Curcumin had been grown, it contains 2-9% of Curcuminoids. Curcuminoids are the group of compounds like Curcumin, Demethoxycurcumin (DMC) and Bisdemethoxycurcumin (BDMC) (fig. 5). All three compounds are almost the same structurally except that Desmethoxycurcumin, Bisdemethoxycurcumin is devoid of methoxy groups which are present in Curcumin. Bisdemethoxycurcumin and desmethoxycurcumin also show anti-cancer activity [103, 105].

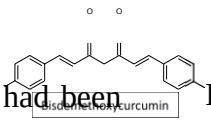


Fig. 5: Structures of curcuminoids [103]

Various strategies were tried by the research scholars to extract and to synthesize Curcumin and its derivatives in the laboratory. S. J Kulkarni gave a detailed procedure for the extraction and purification of Curcuminoids from the rhizome of herb *Curcuma longa*. According to them, Soxhlet extraction is the ideal method using methanol solvent to get high yields [106].

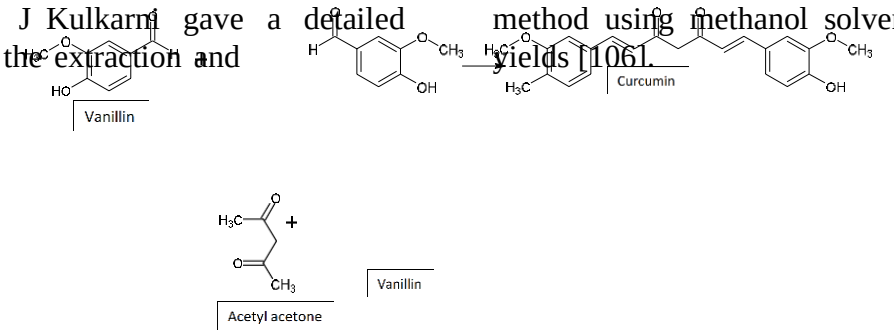


Fig. 6: Schematic presentation for the synthesis of curcumin [107]

H. J. J Pabon synthesized Curcumin in the laboratory by using vanillin, acetylacetone and boric anhydride as catalyst (fig. 6). It was finally concluded that by changing catalyst such as tri-isopropyl borate and tri-sec: Butyl borate, the yield of Curcumin increases [107].

Wehrli and Christof synthesized Curcumin using boric acid, vanillin, m-xylene, acetylacetone, dimethylformamide and benzylamine under different reaction time to increase the yield of Curcumin from 54% for heating for 2 h to 83% for heating for 3 ½ h. In one method, from this reaction mixture, Curcumin was isolated using acetic acid and purified by refluxing with methanol. The final yield was 69%. In another method, ethyl acetate and acetic acid were used to extract Curcumin from the reaction mixture and crystallized using methanol with a final yield of 59%. Another route of synthesis was tried by replacing benzylamine with 1-butyl amine and changing the pressure and temperature parameters compared to the first route. Here, the yield was 68%. In still another route, 1-butylamine was replaced with 2-ethoxymethyl amine and changing the reaction parameters like pressure, temperature etc. obtained the yield of 71% [108]. Lincy Joseph *et al.* synthesized the Curcumin and confirmed the structure of Curcumin by Nuclear Magnetic Resonance (NMR) result. They obtained orange coloured needle- shaped crystals and characterized by NMR, Infra-Red (IR) and Mass spectral analysis [109].

Thus, different authors experimented with various ways to optimize the yield of Curcumin by using numerous reagents and by altering the conditions of the reaction. Researchers tried to find the cause of low bioavailability of Curcumin. They studied the metabolism of Curcumin, trying to find out what happens when Curcumin enters the human body. Manfred Metzler *et al.* reviewed the metabolism of Curcumin [110]. They discussed about the poor systemic bioavailability of Curcumin. In their paper, they mentioned that even after the administration of large doses of Curcumin, their concentrations were not detectable in the plasma or blood or urine. Takanori Tsuda *et al.* summed up the metabolite products of Curcumin. Here, it is mentioned that when Curcumin homogenates with a microsome fraction of human intestinal and liver tissue, the major metabolite is Curcumin glucuronide. When Curcumin was incubated with cytosol fraction, it produces Curcumin sulfate and Hexahydrocurcumin with a minor portion of Tetrahydrocurcumin (fig. 7 and 8) [111].

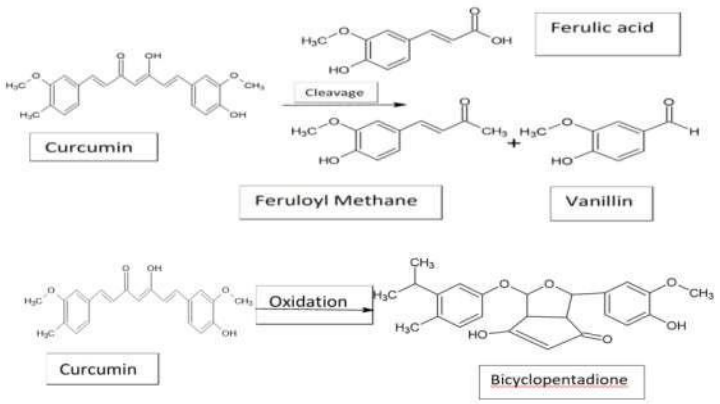


Fig. 7: Degradation pathways of curcumin (cleavage and oxidation) [111]

These reactions suggest that due to the low solubility of Curcumin, its absorption by the body is very less and before Curcumin reaches the target site, it gets metabolised. To overcome these problems, many synthetic and experimental changes (mainly *in vitro*) were carried out by scholars and they were successful up to some extent [111].

Majority of them tried the different mode of delivery and synthesized the analogues of Curcumin. Various nanoparticles of Curcumin like polymer nanoparticles, liposomes, micelles, Solid Lipid Nanoparticles (SLNs) and polymer conjugates have been developed to deliver the drug to the target site. Shengfeng Peng *et al.* prepared Curcumin nanoparticles by pH driven method at various concentrations of biosurfactant and sophorolipid solution. Alkaline Curcumin and acidic sophorolipid solutions were stirred constantly. After incubation of a period, Curcumin nanoparticles were centrifuged. Curcumin nanoparticles were then tested for their bioavailability in different phases. It has been observed that Curcumin becomes soluble in a basic medium and gets a negative charge. Under acidic conditions, Curcumin loses its negative charge and its solubility decreases. This makes it to enter the core of surfactant micelles, which leads to the formation of sophorolipid coated Curcumin nanoparticles increasing the bioavailability of Curcumin [112].

To overcome the limitation of oral Curcumin administration, Suryani *et al.* prepared Curcumin nanoparticles and formulated them into transdermal patches. Results revealed that with an average weight

of 0.7 g, patches contain moisture content from 1.0 to 6.0%. Tensile strength of developed Curcumin nanoparticles transdermal patches was found to be 1.0 to 2.0 N/mm. The authors concluded that developed Curcumin nanoparticles transdermal patches demonstrated good flux values for the penetration of Curcumin nanoparticles into the skin [113].

Mahesh Kharat *et al.* investigated the physical and chemical stability of Curcumin in oil in water emulsion at different pH levels, which indicated that Curcumin emulsions are stable in acidic pH and yellow colour faded in alkaline medium. Thus, it was concluded that emulsion-based delivery systems would be better for the chemical stability and aqueous dispersibility of Curcumin [114]. Review article of Mohammad N. Oskouie *et al.* discussed a novel way for Curcumin delivery. Curcumin was introduced into the human body by two different methods via encapsulation and primed method using exosomes. In the Curcumin-encapsulated method, the drug is loaded onto the exosomes while in the Curcumin-primed method, cells are treated with Curcumin and then Curcumin-exosome is released into the body (fig. 9) [115].

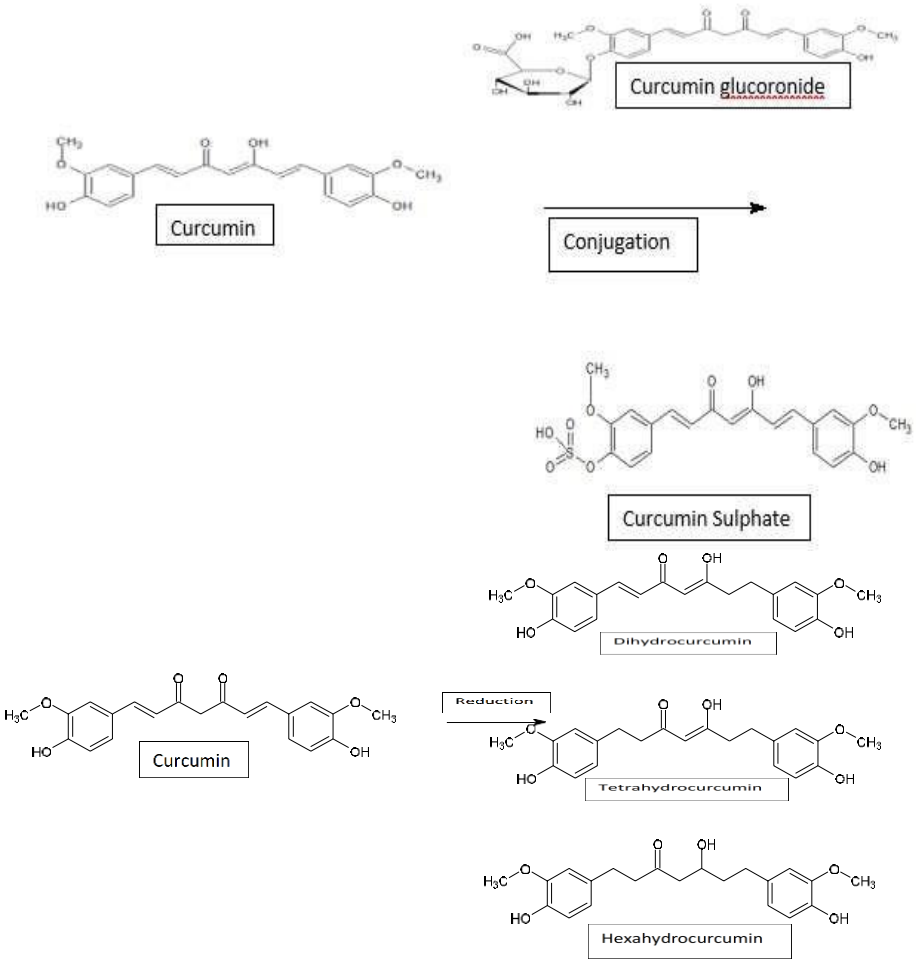


Fig. 8: Metabolism of curcumin (conjugation and reduction) [111]

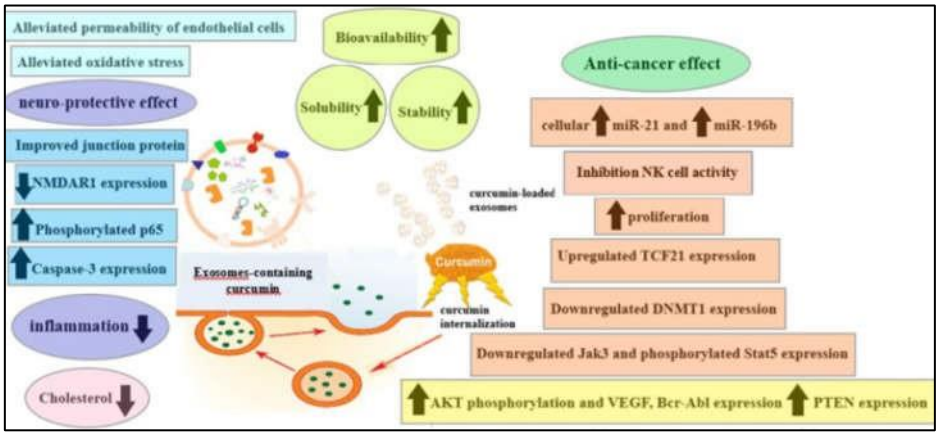


Fig. 9: Delivery of curcumin using exosomes for anticancer activity [115]

Sauraj *et al.* developed Xylan-Curcumin pro-drug, which was self- assembled into nanoparticles for the delivery of Curcumin. It was found to be highly pH-sensitive and releases most of the drug at a lower pH. It demonstrated a higher toxicity than Curcumin [116]. Sreeraj Gopi *et al.* developed liposomal Curcumin powder (LCP) based on nanofiber weaving technology (NFW technology) which increases the bioavailability and stability of Curcumin. Curcumin could be protected from rapid metabolism and reach the target site (fig. 10) [117].

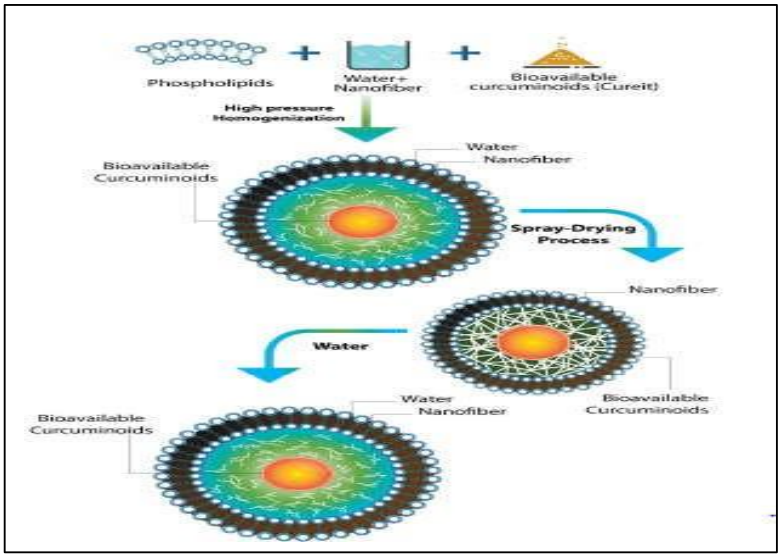


Fig. 10: Preparation of phospholipid vesicle for the delivery of curcuminoids [117]

Sujit *et al.* review paper discussed the Nanocochleates as an oral potential for the delivery of anticancer drugs which can be used as an alternate for delivering the therapeutic or biological agents to cancer cells. In the paper, authors exemplified the various methods to prepare Nanocochleates and mechanisms of drug delivery. In the end, author/s recommended that in the treatment of cancer cells, application of Nanocochleate can progress the effectiveness of chemotherapeutic agents and this novel drug delivery system can push the therapeutic world into the renewed era [118].

Other than different delivery modes, researchers experimented with other options to increase the solubility and bioavailability of Curcumin by synthesising novel compounds. In these experiments, synthetically, they tried to attach various groups to the parent Curcumin and termed as Curcumin derivatives of Curcumin analogue. With the advancement of technology, before synthesizing them, their suitability can be confirmed by a computational tool like molecular docking.

Manouchehr Teymouri *et al.* evaluated the biological and pharmacological properties of Dimethoxy Curcumin (DiMC) as a stable Curcumin analogue. DiMC, a synthetic analogue of Curcumin exhibited superior anti-cancer activity and metabolic stability. DiMC lack phenolic- OH groups as opposed to Curcumin. DiMC exerts unique molecular activities compared to Curcumin, including induction of androgen receptor (AR) degradation and suppression of the transcription factor activator protein-1 (AP-1). Authors concluded that enhanced AR degradation on DiMC treatment suggests it as a novel anticancer agent against resistant tumours with androgenic etiology [119].

Govindharasu Banuppriya *et al.* synthesized

water-soluble Curcumin derivatives containing amine. Synthesized Curcumin derivatives showed cytotoxicity against HeLa cell lines. By immunoblot analysis, it was evidenced that there is induced p53 mediated apoptosis. The compound also showed a good binding property with the DNA of the cell [120]. Papers reported that Octahydrocurcumin (OHC), the final hydrogenated metabolite of Curcumin has potential biological activities. Zhenbiao Zhang *et al.* demonstrated that the anti-tumour activity of OHC was more pronounced than Curcumin. OHC upregulated the p53 expression and down-regulated murine double minute 2 homolog (T) expression. Also, it reduced Bcl-2 and Bcl-xl protein expressions. In ascitic cells, Bax and Bad expressions were increased by OHC. This suggested that hydrogenation of the C7 linker double bonds and the carbonyl groups might afford more potent anti-hepatocellular carcinoma (anti-HCC effect) by upregulating p53 expression and downregulating murine double minute 2 expression [121].

Shivakumar S. Jalde *et al.* synthesized series of Chlorine-6-Curcumin (C- 6-cur) conjugates and tested for their photosensitizing potential against pancreatic cancer cell lines. They confirmed that above compound showed excellent photodynamic therapy (PDT) efficacy with inhibitory concentration 50 (IC50) of 40, 35 and 41 nano Molar (nM) AsPC-1, MIA PaCa-2 and PANC-1 respectively. This compound upregulated the expression of BAX, cytochrome-C and cleaved caspase 9 while downregulating the Bcl-2 expression, an anti-apoptotic protein marker. This compound has the potential to trigger the intrinsic apoptotic pathway in AsPC-1 a pancreatic cancer cell line [122].

Mahin Ramezani *et al.* mentioned that BDMC, a natural analogue, present in the rhizome *Curcuma longa* along with Curcumin, also possess anti- tumour activity. This compound has shown more effective anticancer activity than Curcumin in almost all type of cancers through different pathways [123]. Apoptotic effect of BDMC is induced by reducing the levels of heme oxygenase-1, BCL-2 (an anti-apoptotic protein). BDMC increases the level of ROS. Through mechanistic evaluations, the pro- apoptotic effect is interfered by binding to cannabinoid receptor-2 and there is an activation of downstream effectors like the Fas-dependent death pathway, caspase-8, and caspase-3 [123]. On the same line to increase the effectiveness of Curcumin, scientists tried numerous approaches such as combination therapy. Curcumin is used in the mode of combination therapy with other synthetic, semi-synthetic and natural products along with other mono-therapeutic drugs. In this practice, Curcumin was found to act synergistically and resulting in enhancing the effect of the mono-therapeutic drug. Nano form of Curcumin in combination with synthetic drugs like Cisplatin loaded onto liposomes were tried on hepatic cancer HA22T/VGH cell line both individually and combined. Studies revealed that combination therapy increases the intracellular ROS level, retention time and dramatically improved the anti-tumour effect [124].

Curcumin combined with Erlotinib, Sunitinib and Sorafenib along with Doxorubicin was tested *in vitro* and *in vivo* for their synergistic effects for anti-cancer activity. Among all combinations, Curcumin with Sunitinib displayed the maximum potency. Remaining combinations also presented a better effect than when they had

been administrated alone [125]. Curcumin and Metformin were combined and tested for its anti-proliferative activity against breast cancer cells of mice. The combination treatment unveiled the highest effects against tumour proliferation and growth. It significantly reduced vascular endothelial growth factor (VEGF) expression, induced Tryptophan 53 (Trp53) independent apoptosis, triggered Th2 (T Helper Cell Type 2) immune response and showed no toxicity [126]. Docetaxel is the most used chemotherapeutic agent to target androgen signalling in metastatic prostate cancer (PCa). However, prolonged treatment with Docetaxel results in drug-resistant cancer cells. Curcumin is a non-toxic organic compound with multifaceted chemopreventive potential. The human prostate cancer cell lines- PCa cell lines, DU145 and PC3 were treated with Curcumin and Docetaxel alone and in their different combinations. Authors reported that treatment using a combination of Curcumin and Docetaxel inhibited the proliferation and induced apoptosis significantly higher than the Curcumin and Docetaxel-treated group alone. Interestingly, the combined treatment with Curcumin and Docetaxel modulates the expression of Receptor Tyrosine Kinases (RTKs), Phosphoinositide 3-kinase (PI3K), PKB, also known as Akt, which is a serine/threonine-specific protein kinase (phospho-AKT), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa B), p53, and cyclooxygenase-2 (COX-2). This shows that combination therapy is a boon for cancer patients through complete success is yet very far to be reached [127].

Thus, combination therapy sets a new pathway for treading along the success path and inspire the scientists to put more efforts on natural products, either alone or in combination to increase their bioavailability and efficiency at the target site. In this series, Huarong Huang *et al.* tested combination of α-Tomatine, a glycoalkaloid (phytochemical in tomatoes) and Curcumin on different prostate cancer cells. In results, they stated that combinations of α-tomatine and Curcumin synergistically inhibited the growth and induced apoptosis in prostate cancer PC-3 cells. Effects of the α-tomatine and Curcumin combination were associated with synergistic inhibition of NF-κB activity and a potent decrease in the expression of its downstream gene Bcl-2 in the cells [128].

Quercetin, a natural bio-active compound and Curcumin were applied separately and in combination to human gastric carcinoma cell line (MGC-803) cells by Zhang J. *et al.* Combined treatment with Curcumin and Quercetin resulted in significant inhibition of cell proliferation, accompanied by loss of mitochondrial membrane potential, the release of cytochrome c and decreased phosphorylation of AKT and ERK. Results indicated that the combination of Curcumin and Quercetin induces apoptosis through the mitochondrial pathway [129].

Ergul Mutlu Altunda *et al.* investigated the combination of Quercetin and Curcumin on Chronic Myeloid Leukaemia (K562) Cells. They confirmed that less dose of combined formulation is effective to induce apoptosis via through mitochondrial pathway. It increases the ROS levels and decreases the Glutathione (GSH) levels. Results of messenger Ribonucleic acid (mRNA) and protein expression

suggested that probably cytochrome-c was released from mitochondria, which caused PARP and caspase-9 cleavages [130].

Two compounds Ellagic acid (a polyphenol found in raspberries, walnuts, strawberries) and Curcumin was tested on HeLa cell lines by Ergul Mutlu Altunda *et al.* and it showed better activity synergistically than individually [130]. Curcumin and extracellular matrix in different combinations were studied for their anti-proliferative activity on MCF- 7 (breast cancer cell lines) and found that extracellular matrix proteins boosted the activity of Curcumin [131].

Natural extracts from turmeric, ginger and garlic were tested for their anti-cancer activity against all breast cancer cell lines. The bioactive constituents of these natural extracts without Tamoxifen (a synthetic drug commonly used for breast cancer) induces apoptosis. With Tamoxifen, these extracts showed greater anti- cancer activity than when Tamoxifen was given alone. Authors suggested that there is a possibility that natural extracts may be sensitizing the cancer cells towards Tamoxifen [132].

Though Curcumin and Resveratrol are promising anti-cancer drugs, their low bioavailability and low solubility hinder their therapeutic use. But with an advanced drug delivery system, this drawback could be overcome to a certain extent. This has opened the doors for further exploration [133].

Curcumin and Mannan from *Aloe vera* have shown inhibition of the proliferative activity of immune cells like peripheral blood mononuclear cells (PBMC) or monocytes in the human body. So, these can be used for alternative or complementary medicines quite effectively [134]. In case of colorectal cancer, Curcumin enhanced 5-FU expression of proapoptotic proteins (caspase-8,-9,-3, PARP, and BAX) and simultaneously, it downregulated antiapoptotically (Bcl-xL) and proliferative (cyclin D1) proteins leading to cell death. So, when combined with 5-FU, it mediates apoptosis of resistant cells. Adjuvant chemotherapy with Curcumin and combination of drugs Folinic acid, Fluorouracil and Oxaliplatin (FOLFOX) has been quite successful in the treatment of gastric cancer. Wnt1 gene expression has been shown to decrease in the case of child leukemia patients. Similarly, adjuvant chemotherapy of Curcumin with Doxorubicin or Cisplatin induces cell cycle arrest by initiating the intrinsic apoptotic pathway. Curcumin has been found to be a suitable adjuvant in the treatment of other cancers like cervical and oral cancer as well as sensitizing cancer stem cells, thereby reducing their population [134].

Review article of Abir Kumar Panda *et al.* explains the mechanism of Curcumin to arrest the growth of cancer cells (fig. 11) [135]. Curcumin inhibits ABC transporter function, cell cycle progression, apoptosis, angiogenesis, the expression of anti-apoptotic proteins, multiple cell survival signaling pathways and their cross-communication, and by modulating immune responses. It also induces the initiation of both p53-dependent and p53-independent G2/M phase cell cycle arrest. So, Curcumin can be used either alone or in the form of combination therapy for treating different cancers [135].

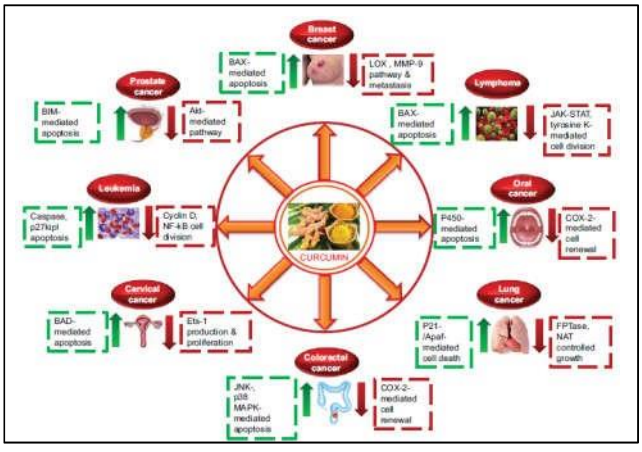


Fig. 11: Cellular pathways affected by curcumin in the treatment of cancer [135]

In different research studies, it has been specified that Curcumin can constrain the interleukin-6 (IL-6)-mediated phosphorylation of Signal transducer and activator of transcription 3 (STAT3) and adept to downregulate the NF-κB, thus the proliferation of cancer cells can be subdued by using Curcumin [136-137]. In the treatment of colorectal cancer cells, Curcumin downregulated the miR-21 gene, which is overexpressed. Curcumin inhibited the activator protein (AP-1) binding to promoter i.e. miR-21 [101]. In the case of HCT 116 colorectal cancer cells, there will be cell cycle arrest in the G/M phase via miR-21 gene regulation. Thus, Curcumin again helps to inhibit the tissue growth of the tumour [138].

In an *in vivo* study of colorectal cancer, the better response was noticed towards radiation therapy after it combined with Curcumin. Author elucidate that it might be due to the ability of Curcumins to target NF-κB [139]. Further research proves that Curcumin in both cases i.e. *in vitro* and *in vivo* is capable to induce apoptosis and inhibit proliferation of prostate cancer [140]. Unambiguously, this is done by meddling with various cellular pathways like nuclear factor κ (NFκB), epidermal growth factor receptor (EGFR), and (MAPK) [141-142]. A recent study has discovered that Curcumin is proficient to activate protein kinase D1 (PKD1), which leads to the dilution of oncogenic signalling by MAPK and β-catenin consequently reticence of prostate cancer [143]. In numerous head and neck carcinomas, particularly STAT3 and NF-κB were found to be overexpressed. *In vitro* studies of Curcumin in different head and neck cancer cell lines have proven to be very positive. Since Curcumin can affect many cellular pathways involved in cell proliferation, it can adequately inhibit cell growth [144].

Combating with brain tumors take diverse cellular pathways, like autophagy, apoptosis, invasion, metastasis and angiogenesis and pervading the blood-brain barrier (BBB) is a major limitation. Neil V. Klinger and Sandeep Mittal have found that Curcumin can arrest G2/M cell cycle arrest in a dose-dependent manner [145-146].

Curcumin can cross the BBB at high levels and it exhibited manifold molecular targets. In an *in vivo* study, human glioma U-87 cells were xenografted into athymic mice. Authors confirmed that Curcumin was competent enough to subdue glioma angiogenesis via impeding Matrix metallopeptidase 9 (MMP-9) and downregulating endothelial cell markers (CD31 and CD105 mRNA [146]. Another research work of Wu B *et al.* stated that in U-251 malignant glioblastoma cells, when Curcumin was used it induces the arrest of G2/M cell cycle by swelling protein kinase 1 (DAPK) [147].

CONCLUSION

Curcumin, a golden drug has been studied widely and still, researchers are appraising this compound for its different therapeutic uses. Curcumin exhibited a wide range of spectrum against numerous types of cancers. Being natural, its efficiency with less or no side effects has been evidenced by many researchers in several clinical trials also, but low bioavailability and less solubility hinder its anticancer activity. To overcome these major issues, several approaches such as combination therapy, diverse drug delivery modes, synthesis of Curcumin derivatives, chemical modification of Curcumin moiety etc. were widely explored by the researchers. Still, there are many gaps which have to be plug by further research. On the other hand, teething troubles with chemical modification and synthesis of Curcumin derivatives like less stability, effectiveness, bioavailability, water-solubility, target delivery, the requirement of high potency for the treatment etc. persists. In general, it has been noticed that to achieve one target; there will be a sacrifice of another target. Thus, there is an urgent need of focusing research work to enhance bioavailability and hydrophilicity of Curcumin, to understand its working mechanism in terms of action and reactions. Lack of clinical studies give enough

opportunity to bring the lab work at the level of clinical trials.

ABBREVIATION

A-549-Adenocarcinomic human alveolar basal epithelial cells, AKT- Protein kinase B (PKB), also known as Akt, is a serine/threonine- specific protein kinase, Akt/mTOR-Intracellular signalling pathway, anti-HCC effect-Anti-hepatocellular carcinoma, AP-1-Activator protein-1, AR-Androgen receptor, AsPc-1-Human pancreatic adenocarcinoma cell line, Bax/-Bcl-2-associated X protein, Bcl-2/- Protein family, Bcl-xl-B-cell lymphoma-extra large, BRAF-Human gene referred to as proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, BxPc-3-Human pancreatic cancer cell line, CD105-Endoglin (CD105) is an accessory receptor, CD31-Platelet endothelial cell adhesion molecule (PECAM-1) also known as cluster of differentiation 31, CDK1-Cyclin-dependent kinase 1, COX-2–Cyclooxygenase-2, CUR–Curcumin, DiMC-Dimethoxy curcumin, DNA-Deoxyribonucleic acid, DU145–Human Prostate cancer cell line, EGFR-Epidermal growth factor receptor, ERK-Extracellular-signal-regulated kinase, FOLFOX-Folinic acid (leucovorin) "FOL", Fluorouracil (5-FU) "F", and Oxaliplatin (Eloxatin) "EX"., 5-FU–5 Fluorouracil, G/M phase–Cell cycle, GSH- Glutathione, HA22T/VGH-Human hepatoma-derived cell line, HCT- 116-Human colon cancer cell line, HeLa cell–Human cervical cancer cell line, HeLa cells-Henrietta Lacks cervical cancer cells, HER-2- Human epidermal growth factor receptor 2, HT-29-Human Colorectal Adenocarcinoma, K562-First human immortalised myelogenous leukemia cell line, LS-174-T-human colon carcinoma cell, MAPK-Microtubule associated protein kinase, MAPK-Mitogen- activated protein kinase, MCF-7-Michigan Cancer Foundation breast cancer cell line, MDA-MB 231-M. D. Anderson-Metastasis Breast cancer-231, MEK–[acronym MEK derives from MAPK/ERK Kinase (Mitogen-activated protein kinase kinase/extracellular-signal-regulated kinase)], MGC-803-Human gastric carcinoma cell line MGC-803, MIA PaCa-2-Human pancreatic cancer cell line, mRNA–Messenger RNA, NCI-H460-Lung cancer cell line H460of the 60 cell lines from National Cancer Institute, NFW–Nanofibre weaving Technology, NF-κB-Nuclear factor kappa-light-chain-enhancer of activated B cells, nM–Nano Molar, p53-Tumor protein, PANC-1– Pancreatic Adenocarcinoma cancer cell line, PARP-Poly (ADP- ribose) polymerase, PC-3-Prostate cancer cell line, PC3-Prostate Cancer cell lines, PCa cell lines–Prostate Cancer cell lines, PDT-Photodynamic therapy, PI3K-Phosphoinositide 3-kinase, ROS– Reactive

Oxygen Species, RTKs–Receptor Tyrosine Kinases, SK-BR- 3-Memorial Sloan–Kettering Cancer Center, STAT3-Signal transducer and activator of transcription 3, TE-8-Human oesophageal cancer cells, Th2-T Helper Cell Type 2, TNF α-Tumor necrosis factor-alpha, VEGF-Vascular endothelial growth factor, Wnt1 gene-Proto-oncogene protein Wnt-1 is a protein, ZR-75– Human Caucasian breast carcinoma cell line.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. Ca-Cancer J Clin 2018;68:7–30.
2. Gupta AP, Pandotra P, Sharma R, Kushwaha M, Gupta S. Marine resource: a promising future for anticancer drugs. Stud Nat Prod Chem 2013;40:229-325.
3. Momna H. Introduction to cancer biology. 2nd ed. Momna Hejmadi and bookboon.com; 2010.
4. Franks LM, Teich NM. Introduction to the cellular and molecular biology of cancer. New York: Oxford University Press; 1997.
5. Raymond WR. Cancer biology. 4th ed. New York: Oxford University Press; 2007.
6. O'Connor CM, Adams JU. Essentials of cell biology. Cambridge (MA): NPG Education; 2010.
7. Evelyn MS. Cancer characteristics and selection of cases. 3rd ed. United States: SEER Publications; 1992.
8. P Carmeliet, Jain RK. Angiogenesis in cancer and other diseases. Nature 2000;407:249–57.
9. Tatiana CL, Luiza CS, Leila SM, Laura BC, Felipe SR, Edmilson OS, *et al.* IKKβ targeting reduces KRAS-induced lung cancer angiogenesis *in vitro* and *in vivo*: a potential anti-angiogenic therapeutic target. Lung Cancer 2019;130:169–78.

10. Hanahan D, Weinberg R. Unique characteristics of cancer cells # 1–cancer cells remain undifferentiated # 2–cancer cells lack normal cell signaling responses loss of contact inhibition: evade apoptosis. Cell 2011;144:646-74.
11. Pizzo P, Poplack D. Principles and practice of paediatric oncology. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2001.
12. Baskar R, Kuo AL, Richard YK. Cancer and radiation therapy: current advances and future directions. Int J Med Sci 2012;9:193-9.
13. Michael CP, Donald CD, Carl EF. Perry's chemotherapy sourcebook. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2012.
14. Sarkar FH, Li Y. Using chemopreventive agents to enhance the efficacy of cancer therapy. Cancer Res 2006;66:3347–51.
15. Oiseth SJ, Aziz MS. Cancer immunotherapy: a brief review of the history, possibilities, and challenges ahead. J Cancer Metastasis Treat 2017;3:250-61.
16. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011;480:480–9.
17. Habib FK, Robinson MR, Stitch SR. Effects of tamoxifen on the binding and metabolism of testosterone by human prostatic tissue and plasma *in vitro*. J Endocrinol 1979;83:369-79.
18. Misra R, Sanjukta A. Human gene therapy: a brief overview of the genetic revolution. J Assoc Physicians India 2013;61:127-33.
19. Altanerova U, Jakubechova J, Benejova K, Priscakova P, Pesta M, Pitule P, *et al.* Prodrug suicide gene therapy for cancer targeted intracellular by mesenchymal stem cell exosomes. Int J Cancer 2019;144:897–908.
20. Künnapuu K, Veiman K, Porosk L, Rammul E, Kiisholts K, Lange U, et al. Tumour gene therapy by systemic delivery of plasmid DNA with cell-penetrating peptides. FASEB BioAdv 2019;1:105–14.
21. Doran SL, Sanja S, Adhikary S, Jared JG, Jia L, Li MK, *et al.* T-cell receptor gene therapy for human papillomavirus-associated epithelial cancers: a first-in-human, phase I/II study. J Clin Oncol 2018;37:2759–68.
22. Umar A, Dunn BK, Greenwald P. Future directions in cancer prevention. Nat Rev Cancer 2012;12:835–48.
23. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, Braud FJ, Larkin J, *et al.* Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371:1877-88.
24. Liu M, Yang X, Liu J, Zhao B, Cai W, Li Y. Efficacy and safety of BRAF inhibition alone versus combined BRAF and MEK inhibition in melanoma: a meta-analysis of randomized controlled trials. Onco Targets Ther 2017;8:32258-69.
25. Gach K, Szymanski J, Pomorska D, Długosz A, Modranka J, Janecki TA. Combined effects of anticancer drugs and new synthetic α-methylene-δ-lactones on MCF-7 cells. Tumor Biol 2015;36:5971-7.
26. Robert N, Leyland JB, Asmar L, Belt R, Ilegbodu D, Loesch D, *et al.* Randomized phase III study of trastuzumab, paclitaxel and carboplatin compared with trastuzumab and paclitaxel in women with HER-2–overexpressing metastatic breast cancer. J Clin Oncol 2020;24:2786-92.
27. Poon C, He C, Liu D, Lu K, Lin W. Self-assembled nanoscale coordination polymers carrying oxaliplatin and gemcitabine for synergistic combination therapy of pancreatic cancer. J Controlled Release 2015;201:90–9.
28. Shi K, Xue B, Jia Y, Yuan L, Han R, Yang F, *et al.* Sustained co- delivery of gemcitabine and cis-platinum via biodegradable thermosensitive hydrogel for synergistic combination therapy of pancreatic cancer. Nano Res 2019;12:1389–99.
29. Huang W, Chen L, Kang L, Jin M, Sun P, Xin X, *et al.* Nanomedicine-based combination anticancer therapy between

nucleic acids and small-molecular drugs. Adv Drug Delivery Rev 2017;115:82–97.
30. Lei M, Shutao G, Michael LC, Qi L. Nanoformulations for combination or cascade anticancer therapy. Adv Drug Delivery Rev 2017;115:3–22.
31. Prakash O, Kumar A, Kumar P, Prakash A. Anticancer potential of plants and natural products: a review. Am J Pharmacol Sci 2013;1:104-15.
32. Patwardhan B, Ashok DB, Chorghade M. Ayurveda and natural products drug discovery. Curr Sci 2004;86:789-99.
33. Jamal A, Siddiqui A, Tajuddin, Jafri MA. Review on gastric ulcer remedies used in Unani system of medicine. Indian J Nat Prod Resour 2006;5:153–9.
34. Krup V, Prakash LH, Harini A. Pharmacological activities of turmeric (*Curcuma longa Linn*): a review. J Homeopathy Ayurvedic Med 2013;2:133.
35. Greenwell M, Rahman PK. Medicinal plants: their use in anticancer treatment. Int J Pharma Sci Res 2015;6:4103–12.
36. Vaghela H, Shah R, Parmar K. Biogenic synthesis of silver nanoparticles using *Bauhinia variegata* bark extract and its antibacterial efficacy. Int J Green Nanotechnol 2017;3:45–9.
37. Amarvani P, Aruna L, Londonkar R. Characterization of phyto- nanoparticles from *Ficus krishnae* for their antibacterial and anticancer activities. Drug Dev Ind Pharm 2017;44:377-84.
38. Capolupo A, Esposito R, Zampella A, Festa C, Riccio R, Tosco A. Determination of gymnemic acid I as a protein biosynthesis inhibitor using chemical proteomics. J Nat Prod 2017;80:909−15.
39. Chandran S, Ponnusamy T, Bheeman D, Kumar RR, Bellan CS. Dextran sulfate stabilized silver nanoparticle: next-generation efficient therapy for cancer. Int J Appl Pharm 2020;12:59-63.
40. Kumar VS, Reddy RB, Subbaiah GP, Kumar SS, Gurava AV. Anti- cancer potential of a mix of natural extracts of turmeric, ginger and garlic: a cell-based study. Egyptian J Basic Appl Sci 2017;4:332-44.
41. Gupta AP, Khan S, Manzoor MM, Yadav AK, Gupta RA. Anticancer curcumin: natural analogues and structure-activity relationship. Stud Nat Prod Chem 2017;54:335–401.
42. Goel A, Kunnumakkara AB. Curcumin as "Curecumin": from kitchen to clinic. Biochem Pharmacol 2008;75:787–809.
43. Alibeiki F, Jafari N, Karimi MP. Potent anti-cancer effects of less polar Curcumin analogues on gastric adenocarcinoma and esophageal squamous cell carcinoma cells. Biosci Rep 2017;7:1–9.
44. Nagahama K, Utsumi T, Kumano T, Maekawa S, Oyama NK. Discovery of a new function of curcumin which enhances its anticancer therapeutic potency. Biosci Rep 2016;6:1–14.
45. Aggarwal BB, Deb LP. Curcumin differs from tetrahydroCurcumin for molecular

targets, signaling pathways and cellular responses. Molecules 2014;20:85–205.
46. Kunnumakkara AB, Bordoloi D, Padmavathi G, Monisha J, Roy NK, Prasad SA. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. Br J Pharmacol 2017;174:1325–48.
47. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. Cancer Lett 2008;267:133–64.
48. Biji TK, Singh A, Hiroyuki M. Improving the solubility and pharmacological efficacy of curcumin by heat treatment. Assay Drug Dev Technol 2007;5:567–76.
49. Anand P, Kunnumakkara AB, Robert AN, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharma 2007;4:807–18.
50. Wen S, Shen W, Zhao W, Chuanhong W, Shuhui G, Tao H, *et al.* Chemical constituents and biological research on plants in the genus curcuma. Crit Rev Food Sci Nutr 2016;57:1–392.
51. Wan-Ibrahim WI, Sidik K, Kuppusamy UR. A high antioxidant level in edible plants is associated with genotoxic properties. Food Chem 2010;122:1139–44.
52. Angel GR, Nirmala M, Vimala BN. Essential oil composition of eight starchy curcuma species. Phytopharmacology 2013;4:96–105.
53. Venugopalan P, Mohan S, Deepthi TV. Biochemical studies on *Curcuma amada* extracts. Arch Appl Sci Res 2014;6:229–34.
54. Lee YL, Weng CC, Mau JL. Antioxidant properties of ethanolic and hot water extracts from the rhizome of *Curcuma aromatica*. J Food Biochem 2007;31:757–71.
55. Dhal Y, Deo B, Sahu RK. Comparative antioxidant activity of non-enzymatic and enzymatic extracts of *Curcuma caesia* roxb, an important medicinal plant. J Biotechnol 2012;7:17–22.
56. Boonmee A, Srisomsap C, Karnchanatat A, Sangvanich P. Biologically active proteins from *Curcuma comosa* roxb. rhizomes. J Med Plants Res 2011;5:5208–15.
57. Saputri FC, Jantan I. Effects of selected medicinal plants on human low-density lipoprotein oxidation, 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and human platelet aggregation. J Med Plants Res 2011;5:6182–91.
58. Rajan I, Rabindran R, Jayasree PR, Kumar PR. Antioxidant potential and oxidative DNA damage preventive activity of unexplored endemic species of Curcuma. Indian J Exp Biol 2014;52:133–8.

59. Zhang DM, Li Q, Ma DW, Zhang DY, Li F. Study on antifungal activity of oil from curcuma kwangsiensis. Anhui Daxue Xuebao Ziran Kexueban 2008a;32:81–4.
60. Vankar PS. Effectiveness of antioxidant properties of fresh and dry rhizomes of *Curcuma longa* (long and short varieties) with dry turmeric spice. Int J Food Eng 2008;4:10.
61. Manda KR, Adams C, Ercal N. Biologically important thiols in aqueous extracts of spices and evaluation of their *in vitro* antioxidant properties. Food Chem 2009;118:589–93.
62. Dinesha R, Thammanna GS, Harsha R, Srinivas L. Antioxidant and antimicrobial activity of partially purified protein from hot water extract of turmeric (*Curcuma longa* L). Pharmacologyonline 2010;1:996–1004.
63. Ramadas D, Srinivas A. Antioxidant effects of 28 kDa antioxidant protein from turmeric (*Curcuma longa* L). Asian J Pharm Clin Res 2011;4 Suppl 1:75–9.
64. Chandrasekaran CV, Sundarajan K, Edwin JR, Gururaja GM, Mundkinajeddu D, Agarwal A. Immune-stimulatory and anti- inflammatory activities of *Curcuma longa* extract and its polysaccharide fraction. Pharmacogn Res 2013;5:71–9.
65. Madan B, Gade WN, Ghosh B. Curcuma longa activates NF-kappa B and promotes adhesion of neutrophils to human umbilical vein endothelial cells. J Ethnopharmacol 2001;75:25–32.
66. Mohankumar S, McFarlane JR. An aqueous extract of Curcuma longa (turmeric) rhizomes stimulates insulin release and mimics insulin action on tissues involved in glucose homeostasis *in vitro*. Phytother Res 2011;25:396–401.
67. Azuine MA, Kayal JJ, Bhide SV. Protective role of aqueous turmeric extract against mutagenicity of direct-acting carcinogens as well as benzo[α]pyrene-induced genotoxicity and carcinogenicity. J Cancer Res Clin Oncol 1992;118:447–52.
68. Jin SR, Hong JH, Jung SH, Cho KH. Turmeric and laurel aqueous extracts exhibit *in vitro* anti-atherosclerotic activity and *in vivo* hypolipidemic effects in a zebrafish model. J Med Food 2011;14:247–56.
69. Zhang W, Liu D, Wo X, Zhang Y, Jin M, Ding Z. Effects of *Curcuma longa* on proliferation of cultured bovine smooth muscle cells and on expression of low density lipoprotein receptor in cells. China Med J 1999;112:308–11.
70. Rafatullah S, Tariq M, Al-Yahya MA, Mossa JS, Ageel AM. Evaluation of turmeric (*Curcuma longa*) for gastric and duodenal antiulcer activity in rats. J Ethnopharmacol 1990;29:25–34.
71. Chander H, Kulkarni SG, Berry SK. Effectiveness of turmeric powder and mustard oil as protectants in stored milled rice against the rice weevil *Sitophilus oryzae*. Int Pest Control 1991;33:94–7.
72. Prakash D, Suri S, Upadhyay G, Singh BN. Total phenol, antioxidant and free radical scavenging activities of some medicinal plants. Int J Food Sci Nutr 2007;58:18–28.
73. Idris NA, Nor FM, Ismail R, Mohamed S, Hassan CZ. Antioxidative acivity of Malaysian herb extracts in refined, bleached and deodorized palm olein. J Oil Palm Res 2008;20:517–26.
74. Jacob JN, Toloue M. Biological studies of turmeric oil, part 1:selective *in vitro* anticancer activity of turmeric oil (TO) and TO-paclitaxel combination. Nat Prod Commun 2013;8:807–10.
75. Yan W, Bowen WD, Hopson R, Mathew AE, Jacob JN. Biological studies of turmeric oil, part 2: isolation and characterization of turmeric oil components; cytotoxic activity against pancreatic cancer cells. Nat Prod Commun 2013;8:811–4.
76. Chan EW, Lim YY, Wong LF, Lianto FS, Wong SK, Lim KK, *et al.* Antioxidant and tyrosinase inhibition properties of leaves and rhizomes of ginger species. Food Chem 2008;109:477–83.
77. Sukari MA, Wah TS, Saad SM, Rashid NY, Rahmani M, Lajis NH, *et al.* Bioactive

sesquiterpenes from *Curcuma ochrorhiza* and *Curcuma heyneana*. Nat Prod Res 2010;24:838–45.

78. Li H, Wei Y, Long Z, Huang Y, Cui J. Activity and chemical component analysis of the hexane extract from *Curcuma phaeocaulis* against pathogenic fungi. Sichuan Daxue Xuebao Ziran Kexueban 2011;48:191–5.
79. Chen IN, Chang CC, Ng CC, Wang CY, Shyu YT, Chang TL. Antioxidant and antimicrobial activity of zingiberaceae plants in taiwan. Plant Foods Hum Nutr (NY, NY, US) 2008;63:15–20.
80. Lou Y, Xiang Z, Chen R, Li L, Gao H, Li X. Antioxidant activities *in vitro* of different solvent extracts from curcuma wenyujin root tubers. Shipin Kexue (Beijing, China) 2012;33:39–43.
81. Qader SW, Abdulla MA, Chua LS, Najim N, Zain MM, Hamdan S. Antioxidant, total phenolic content and cytotoxicity evaluation of selected Malaysian plants. Molecules 2011;16:3433–43.
82. Ullah HM, Zaman S, Juhara F, Akter L, Tareq SM, Masum EH, *et al*. Evaluation of antinociceptive, *in vivo* and *in vitro* anti- inflammatory activity of ethanolic extract of curcuma zedoaria rhizome. BMC Complementary Altern Med 2014;14:346.
83. Hong CH, Hur SK, Oh OJ, Kim SS, Nam KA, Lee SK. Evaluation of natural products on inhibition of inducible cyclooxygenase (COX-2) and nitric oxi de synthase (iNOS) in cultured mouse macrophage cells. J Ethnopharmacol 2002;83:153–9.
84. Lu B, Yu L, Xu L, Chen H, Zhang L, Zeng Y. The effects of radix curcumae extract on expressions of VEGF, COX-2 and PCNA in gastric mucosa of rats fed with MNNG. Curr Pharm Biotechnol 2010;11:313–7.
85. Hadem KL, Sen A. Curcuma species: a source of anticancer drugs. J Tumor Med Prevention 2017;1:34-140.
86. Policegoudra RS, Chandrasekhar R, Aradhya SM, Singh L. Cytotoxicity, platelet aggregation inhibitory and antioxidant activity of *Curcuma amada* roxb. Extracts Food Technol Biotechnol 2011;49:162-8.
87. Gonzalzez MA, Mancebo AJ, Tangarife CV. Synthesis and biological evaluation of (þ)-labdadienedial, derivatives and precursors from (þ)-sclareolide. Eur J Med Chem 2010;45:4403-8.
88. Bing H, Shen K, An H, Wu Y, Du Q. Aqueous extract of *Curcuma aromatica* induces apoptosis and G2/M arrest in human colon carcinoma LS-174-T cells independent of p53. Cancer Biother Radiopharm 2011;26:97-104.
89. Li Y, Wo JM, Liu Q, Li XM. Chemoprotective effects of *Curcuma aromatica* on esophageal carcinogenesis. Ann Surg Oncol 2009;16:515-23.

90. Shaikh AM, Shrivastava B, Apte KG, Parab PB. *In vitro* screening of some medicinal plants on breast, ovary and colon cancer cell lines. Int J Pharma Bio Sci 2016;7:11-7.
91. Mohammad P, Nosratollah Z, Mohammad R, Abbas JR. The inhibitory effect of *Curcuma longa* extract on telomerase activity in A549 lung cancer cell line. Afr J Biotechnol 2010;9:912-91.
92. Karsono AH, Mayasari O, Tandrasasmita TR. Molecular effects of bioactive fraction of *Curcuma mangga* (DLBS4847) as a down regulator of 5α-reductase activity pathways in prostatic epithelial cells. Cancer Manage Res 2014;6:267-78.
93. Rouhollahi E, Moghadamtousi SZ, Al HN, Kunasegaran T, Hasanpourghadi M. The chemopreventive potential of *Curcuma purpurascens* rhizome in reducing azoxymethaneinduced aberrant crypt foci in rats. BMC Complementary Altern Med 2015;15:15.
94. Hong SL, Lee GS, Syed AR, Abdalla AH, Khalijah A, Nurfina AN, *et al.* Essential oil content of the rhizome of curcuma purpurascens Bl. (Temu Tis) and its anti-proliferative effect on selected human carcinoma cell lines. Sci World J 2014;7:1-7.
95. Oon FS, Nallappan M, Tee TT, Shohaimi S, Kassim NK, Mohd SF, *et al.* Xanthorrhizol: a review of its pharmacological activities and anticancer properties. Cancer Cell Int 2015;15:100.
96. Seo WG, Hwang JC, Kang SK, Jin UH, Suh SJ, Moon SK, *et al.* Suppressive effect of Zedoariae rhizoma on pulmonary metastasis of B16 melanoma cells. J Ethnopharmacol 2005;101:249-57.
97. Pal P, Prasad AK, Chakraborty M, Haldar S, Majumder P, Haldar PK. Evalaution of anticancer potential of methanol extract of *Curcuma zedoaria*. Asian J Pharm Clin Res 2015;7:309-13.
98. Tanzeela N, Muneeb I, Ahmad R, Madiha SF. Turmeric: a promising spice for phytochemical and antimicrobial activities. Am Eurasian J Agric Environ Sci 2015;15:1278–88.
99. Prasad S, Bharat BA. Turmeric, the golden spice: from traditional medicine to modern medicine. In: Benzie IF, Wachtel GS. editors. Herbal medicine: biomolecular and clinical aspects. 2nd ed. Boca Raton (FL): CRC Press/Taylor and Francis; 2011.
100. Grykiewicz G, Silfirski P. Curucmin and curcuminoids in quest for medicinal status. Acta Biochim Pol 2012;59:201–12.

101. Kocaadam B, Şanlier N. Curcumin, an active component of turmeric (*Curcuma longa*) and its effects on health. Crit Rev Food Sci Nutr 2015;57:2889–95.
102. Esatbeyoglu T, Huebbe P, Ernst I, Chin D, Wagner A, Rimbach G. Curcumin-from molecule to biological function. Angew Chem 2012;51:5308-32.
103. Gupta SC, Prasad S, Kim J, Patchva S, Webb L, Priyadarsini KI, *et al.* Multitargeting by curcumin as revealed by molecular interaction studies. Nat Prod Rep 2011;28:1937–55.
104. Priyadarsini KI. Chemical and structural features influencing the biological activity of curcumin chemical and structural features influencing the biological activity of curcumin. Curr Pharm Des 2013;19:2093-100.
105. Priyadarsini KI. Photochemistry reviews photophysics, photochemistry and photobiology of curcumin: studies from organic solutions, bio-mimetics and living cells. J Photochem Photobiol 2009;10:81–95.
106. Kulkarni SJ, Maske KN, Budre MP, Mahajan RP. Extraction and purification of curcuminoids from turmeric (*Curcuma longa* L). Int J Pharmacol Pharm Technol 2012;1:81-4.
107. Pabon HJ. A synthesis of curcumin and related compounds. Recl Trav Chim Pays Bas 1964;83:379–86.
108. C Wehrli. World intellect. Prop Organ Int Bur WO 110168; 2007.
109. Joseph L, George M, Dheeraj MM. Synthesis and spectral characterization of curcumin and related curcuminoids. Pharm Chem J 2016;3:39–44.
110. Metzler M, Pfeiffer E, Schulz SI, Dempe JS. Review article: curcumin uptake and metabolism. Biofactors 2012;39:14-20.
111. Tsuda T. Curcumin as a functional food-derived factor: degradation products, metabolites, bioactivity, and future perspectives. Food Funct 2018;9:705–14.
112. Shengfeng P, Li Z, Zou L, Liu WC, McClements DJ. Enhancement of curcumin bioavailability by encapsulation in sophorolipid- coated nanoparticles: an *in vitro* and *in vivo* study. J Agric Food Chem 2018;66:1488–97.
113. Suryani WA, Musnina OS, Ruslin, Nisa M, Aprianti R, Hasanah M, et al. Formulation and physical characterization of curcumin nanoparticle transdermal patch. Int J Appl Pharm 2019;11:217-21.
114. Kharat M, Du Z, Zhang G, Mcclements DJ. Physical and chemical stability of Curcumin in aqueous solutions and emulsions: impact of pH, temperature, and molecular environment. J Agric Food Chem 2017;65:1525−32.
115. Oskouie MN, Moghaddam BE, Alexandra NS, Zamani, Parvin AS. Therapeutic use of curcumin-encapsulated and curcumin-primed exosomes. J Cell Physiol 2018;234:1–10.
116. Sauraj S, Kumar U, Kumar V, Priyadarshi R, Gopinath P. pH responsive prodrug nanoparticles based on xylan-curcumin conjugate for the efficient delivery of curcumin in cancer therapy. Carbohydr Polym 2018;188:252–9.
117. Sreeraj G, Augustine A, Joby JN, Sabu TQ. Preparation, characterization and *in vitro* study of liposomal curcumin powder by cost effective nanofiber weaving technology. New J Chem 2018;7:1–37.
118. Nayek S, Venkatachalam A, Choudhury S. Recent nanocochleate drug delivery system for cancer treatment: a review. Int J Curr Pharm Res 2019;11:28-32.
119. Teymouri M, Barati N, Pirro M. Biological and pharmacological evaluation of dimethoxy curcumin: a metabolically stable curcumin analogue with a promising therapeutic potential. J Cell Physiol 2016;233:1–39.
120. Banuppriya G, Shakambari G, Sribalan R, Varalakshmi P, Padmini V. Evaluation of anticancer activity of water-soluble curcumin through the induction of apoptosis by p53 and p21 modulation. Chem Select 2018;3:2976–81.
121. Zhang Z, Luo D, Xie J, Lin G, Liu W, Li H, *et al.* Octahydro curcumin, a final hydrogenated metabolite of curcumin,

possesses superior anti-tumor activity through induction of cellular apoptosis. Food Funct 2018;9:2005-14.

122. Jalde SS, Kumar A, Hoon J, Kumar P. Synthesis of novel chlorin e6- curcumin conjugates as photosensitizers for photodynamic therapy against pancreatic carcinoma. Eur J Med Chem 2018;147:66–76.
123. Ramezani M, Hatamipour M, Sahebkar A. Promising anti-tumor properties of bisdemethoxy curcumin: a naturally occurring curcumin analogue. J Cell Physiol 2018;233:880–7.
124. Cheng Y, Zhao P, Wu S, Yang T, Chen Y, Xiaojuan, *et al.* Cisplatin and curcumin co-loaded nano-liposomes for the treatment of hepatocellular carcinoma. Int J Green Pharm 2018;545:261–73.
125. Chen S, Liang Q, Xie S, Liu E, Yu Z, Sun L, *et al.* Curcumin based combination therapy for anti-breast cancer: from *in vitro* drug screening to *in vivo* efficacy evaluation. Front Chem Sci Eng 2016;10:383–8.
126. Falah RR, Talib WH, Shbailat SJ. Combination of metformin and curcumin targets breast cancer in mice by angiogenesis inhibition, immune system modulation and induction of p53 independent apoptosis. Ther Adv Med Oncol 2017;9:235–52.
127. Banerjee S, Santosh KS, Indrajit C, James WL, Singh R. Combinatorial effect of Curcumin with docetaxel modulates apoptotic and cell survival molecules in prostate cancer. Front Biosci Elite Ed 2017;9:235–45.
128. Huarong H, Xuan C, Dongli L, Yan H, Yu L, Zhiyun D, *et al.* Combination of α-tomatine and curcumin inhibits growth and induces apoptosis in human prostate cancer cells. PLoS One 2015;10:1-15.
129. Zhang J, Lin M, Zhou M, Yi T, Tang Y, Tang S, *et al.* Combinational treatment of curcumin and quercetin against gastric cancer MGC-803 cells *in vitro*. Molecules 2015;20:11524–34.
130. Ergul MA, Ayşe MY, Semra KT, Yalçın S. Synergistic induction of apoptosis by quercetin and curcumin in chronic myeloid leukemia (K562) cells. Nutr Cancer 2018;70:1-12.
131. Regassa BL, Vaidya A. Curcumin and extracellular matrix proteins synergistically act to inhibit the proliferation of breast cancer cells. Breast Cancer Manage 2016;5:14.
132. Vemuri S, Banala R, Subbaiah G, Srivastava S, Reddy G, Malarvili
T. Anti-cancer potential of a mix of natural extracts of turmeric, ginger and garlic: a cell-based study. Egyptian J

Basic Appl Sci 2017;4:332-44.

133. Shindikar A, Singh A, Nobre M, Kirolikar S. Curcumin and resveratrol as promising natural remedies with nanomedicine approach for the effective treatment of triple negative breast cancer. J Oncol 2016;16:13.
134. Gandhi DM. Immuno-modulatory effect of turmeric (*Curcuma longa*) and aloe vera on cultured polymorphonuclear cells (PMN) and adherent mononuclear cells. Web Med Central Altern Med 2016;7:1–7.
135. Panda AK, Chakraborty D, Sarkar I, Khan T, Sa G. New insights into therapeutic activity and anticancer properties of curcumin. J Exp Pharmacol 2017;9:31–45.
136. Chakravarti N, Myers JN. Targeting constitutive and interleukin-6-inducible signal transducers and activators of transcription 3 pathway in head and neck squamous cell carcinoma cells by curcumin (diferuloylmethane). Int J Cancer 2006;19:1268–75.
137. LoTempio MM, Veena MS, Steele HL, Ramamurthy B, Ramalingam TS, Cohen AN, *et al.* Curcumin suppresses growth of head and neck squamous cell carcinoma. Clin Cancer Res 2005;11:6994–7002.
138. Mudduluru G, George William JN, Muppala S, Asangani IA, Kumarswamy R, Nelson LD. Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer. Biosci Rep 2011;31:185–97.
139. Kunnumakkara AB, Diagaradjane P, Guha S, Deorukhkar A, Shentu S, Aggarwal BB. Curcumin sensitizes human colorectal cancer xenografts in nude mice to gamma-radiation by targeting nuclear factor-kappaB-regulated gene products. Clin Cancer Res 2008;14:2128–36.
140. Dorai T, Cao YC, Dorai B, Buttyan RK. Therapeutic potential of curcumin in human prostate cancer. Curcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells *in vivo*. Prostate 2001;47:293– 303.
141. Mukhopadhyay A, Bueso Ramos C, Chatterjee D, Pantazis PA. Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines. Oncogene 2001;20:7597–609.

142. McCarty MF. Targeting multiple signaling pathways as a strategy for managing prostate cancer: multifocal signal modulation therapy. Integr Cancer Ther 2004;3:349–80.
143. Sundram V, Chauhan SC. Emerging roles of protein kinase D1 in cancer. Mol Cancer Res 2011;9:985–96.
144. Chun KS, Keum YS, Han SS, Song YS, Kim SH. Curcumin inhibits phorbol esterinduced expression of cyclooxygenase-2 in mouse skin through suppression of extracellular signalregulated kinase activity and NF-kappaB activation. Carcinogenesis 2003;24:1515–24.
145. Klinger NV, Mittal S. Therapeutic potential of curcumin for the treatment of brain tumors. Oxid Med Cell Longevity 2016;2016:1-14.
146. Perry MC, Demeule M, Regina A, Moumdjian RB. Curcumin inhibits tumor growth and angiogenesis in glioblastoma xenografts. Mol Nutr Food Res 2010;54:1192–201.
147. Wu B, Yao H, Wang SX. DAPK1 modulates a curcumin-induced G2/M arrest and apoptosis by regulating STAT3, NF-κB, and caspase-3 activation. Biochem Biophys Res Commun 2013;434:75–80.