CHAPTER 1

INTRODUCTION

1.1. DEFINITION OF NUTRACEUTICALS

Nutraceuticals can be defined as, "a food or part of a food that provides medical or health benefits, including the prevention and / or treatment. Nutraceuticals must not only supplement the diet but should also aid in the prevention and / or treatment of disease and/or disorder". The term "nutraceutical" was coined from "nutrition" and "pharmaceutical" in 1989 by Stephen DeFelice\textsuperscript{1}. About 2000 years ago, Hippocrates correctly emphasized “Let food be your medicine and medicine be your food". Currently, there is an increased global interest due to the recognition that “nutraceuticals” play a major role in health enhancement. There are several definitions for nutraceuticals each of them describes the different attributes of nutraceuticals.

Nutraceuticals can be defined as nonspecific biological therapies used to promote wellness, prevent malignant processes and control symptoms.

Fig. 1.1. A graphical representation of nutraceuticals
Nutraceuticals can also be defined as natural bioactive, chemical compounds that have health promoting, disease preventing and / or medicinal properties.

Most of the nutraceuticals have multiple bioactive compounds, which are used to prevent or control the disease or symptom of the disease. The use of nutraceuticals, as an attempt to achieve desirable beneficial outcomes with reduced side effects, as compared to other therapeutic agents\textsuperscript{2,3}. The preference for the discovery and production of nutraceuticals over pharmaceuticals is well seen in pharmaceutical and biotechnology companies.

1.2. CATEGORIES OF NUTRACEUTICALS

Nutraceuticals can be grouped into the following three broad categories\textsuperscript{4}:

1. Substances with established nutritional functions such as vitamins, minerals, amino acids and fatty acids - Nutrients
2. Herbs or botanical products as concentrates and extracts - Herbals
3. Reagents derived from other sources (e.g. pyruvate, chondroitin sulphate, steroid hormone precursors) serving specific functions such as sports nutrition, weight-loss supplements and meal replacements – Dietary supplements

Out of these three categories, “the herbs and botanical herbs or botanical products as concentrates and extracts” are the important category for chemists, due to the vast application i.e., identification of essence compound of a nutraceutical, application of lead compound towards the SAR based drug discovery.
1.3. NUTRACEUTICAL MARKET

Nutraceutical and functional food ingredients are ingredients with human health benefits beyond basic nutrition. The Indian nutraceutical market in 2007 was INR 18.75 billion and expected to grow by 20%. The global nutraceutical market was US$ 117.3 billion in 2007, where as in 2008, it was US$ 123.9 billion. Global nutraceutical market is projected to grow US$ 147 billion by 2010. It is expected that nutraceutical market will reach US$ 176.7 billion in 2013 with a CAGR 7.4%. The United States has been the major market for nutraceuticals. India and China are becoming fastest growing markets. Vitamins, minerals and nutrients constitute about 85% of the market while antioxidants and anti-agents account for 10% and herbal extracts occupy 5% of the market globally.

Pharmaceutical companies are now adopting the nutraceuticals due to the overwhelming response of the customers as well as the less expensive and time consuming nutraceuticals research process in drug discovery.

1.4. THE LIST OF IMPORTANT NUTRACEUTICALS

The list of nutraceuticals is very vast and the list is increasing everyday. The nutraceuticals under category I such as vitamins, minerals, amino acids and fatty acids have established chemistry and biological activity and thus not discussed here. This is a list of important nutraceuticals of category II found in our regular diet.

<table>
<thead>
<tr>
<th>Sl.No.</th>
<th>Herbal origin</th>
<th>Nutraceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Catechu</td>
<td>Catechins, epicatechin</td>
</tr>
<tr>
<td>2</td>
<td>Garlic</td>
<td>Alliin</td>
</tr>
<tr>
<td></td>
<td>Plant Name</td>
<td>Chemicals</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>3</td>
<td>Aloe</td>
<td>Polysaccharides</td>
</tr>
<tr>
<td>4</td>
<td>Galangal</td>
<td>Shagoal</td>
</tr>
<tr>
<td>5</td>
<td>Andrographis</td>
<td>Andrographolides</td>
</tr>
<tr>
<td>6</td>
<td>Asparagus</td>
<td>Saponins</td>
</tr>
<tr>
<td>7</td>
<td>Belladonna</td>
<td>Atropine</td>
</tr>
<tr>
<td>8</td>
<td>Margosa tree</td>
<td>Bitters</td>
</tr>
<tr>
<td>9</td>
<td>Thyme-leaved gratiola</td>
<td>Bacosides</td>
</tr>
<tr>
<td>10</td>
<td>Seakale beet</td>
<td>Betaines</td>
</tr>
<tr>
<td>11</td>
<td>Silk Cotton Tree</td>
<td>Boswellic acid</td>
</tr>
<tr>
<td>12</td>
<td>Green Tea</td>
<td>Polyphenols</td>
</tr>
<tr>
<td>13</td>
<td>Senna</td>
<td>Sennosides</td>
</tr>
<tr>
<td>14</td>
<td>Climbing Staff tree</td>
<td>Alkaloids</td>
</tr>
<tr>
<td>15</td>
<td>Gotu Kola</td>
<td>Asiatic Acid, Asiaticosides</td>
</tr>
<tr>
<td>16</td>
<td>Veld grape</td>
<td>Ketosterones</td>
</tr>
<tr>
<td>17</td>
<td>Coleus</td>
<td>Forskohlin</td>
</tr>
<tr>
<td>18</td>
<td>Indian Bedellium</td>
<td>Guggalsterones</td>
</tr>
<tr>
<td>19</td>
<td>Turmeric, Indian Saffron</td>
<td>Curcuminoids</td>
</tr>
<tr>
<td>20</td>
<td>Indian Gooseberry</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>21</td>
<td>Indian Gooseberry</td>
<td>Tannins</td>
</tr>
<tr>
<td>22</td>
<td>Indian Gooseberry</td>
<td>Ellagic acid</td>
</tr>
<tr>
<td>23</td>
<td>Whitehead</td>
<td>Bitters</td>
</tr>
<tr>
<td>24</td>
<td>Jambul, Rose Apple</td>
<td>Saponins, Alkaloids</td>
</tr>
<tr>
<td>25</td>
<td>Garcinia</td>
<td>HCA</td>
</tr>
<tr>
<td>26</td>
<td>Mangosteen</td>
<td>Mangostin</td>
</tr>
<tr>
<td></td>
<td>Name</td>
<td>Active Constituent</td>
</tr>
<tr>
<td>---</td>
<td>-------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>27</td>
<td>Liquorice, Sweet Root</td>
<td>Glycyrrhizin</td>
</tr>
<tr>
<td>28</td>
<td>Liquorice, Sweet Root</td>
<td>Deglycyrrhizinated</td>
</tr>
<tr>
<td>29</td>
<td>Small Indian Ipecacuanha,</td>
<td>Gymnemic acid</td>
</tr>
<tr>
<td>30</td>
<td>Bitter Gourd</td>
<td>Bitters, Charantin</td>
</tr>
<tr>
<td>31</td>
<td>Cow Itch Plant</td>
<td>L-DOPA</td>
</tr>
<tr>
<td>32</td>
<td>Holy Basil, St. Joseph Wort</td>
<td>Tannins</td>
</tr>
<tr>
<td>33</td>
<td>Kidney Bean</td>
<td>Activity 8000 units</td>
</tr>
<tr>
<td>34</td>
<td>Indian Long Pepper</td>
<td>Piperine</td>
</tr>
<tr>
<td>35</td>
<td>Black Pepper</td>
<td>Piperine</td>
</tr>
<tr>
<td>36</td>
<td>Indian Kino Tree</td>
<td>Pterostillbene, Flavones</td>
</tr>
<tr>
<td>37</td>
<td>Pomegranate</td>
<td>Ellagic acid</td>
</tr>
<tr>
<td>38</td>
<td>Kotalahimbatu</td>
<td>Saponins, Flavones</td>
</tr>
<tr>
<td>39</td>
<td>Soapnut-tree</td>
<td>Saponins</td>
</tr>
<tr>
<td>40</td>
<td>Arjuna</td>
<td>Tannins, Arjunic acid</td>
</tr>
<tr>
<td>41</td>
<td>Belleric myroblan</td>
<td>Tannins</td>
</tr>
<tr>
<td>42</td>
<td>Chebulic myroblan</td>
<td>Tannins</td>
</tr>
<tr>
<td>43</td>
<td>Tinospora Gulancha</td>
<td>Bitters</td>
</tr>
<tr>
<td>44</td>
<td>Small Caltrops</td>
<td>Saponins</td>
</tr>
<tr>
<td>45</td>
<td>Fenugreek</td>
<td>Saponins</td>
</tr>
<tr>
<td>46</td>
<td>Fenugreek</td>
<td>4-hydroxyisoleucine</td>
</tr>
<tr>
<td>47</td>
<td>Bellirica myrobalan, Chebulic Myrobalan &amp; Indian Gooseberry</td>
<td>Tannins</td>
</tr>
<tr>
<td>48</td>
<td>Valerian rhizome</td>
<td>Valeric acid</td>
</tr>
<tr>
<td>49</td>
<td>Winter Cherry</td>
<td>Withanolides</td>
</tr>
<tr>
<td>50</td>
<td>Ginger</td>
<td>Gingerols</td>
</tr>
</tbody>
</table>
1.5. THE ESSENTIAL NUTRACEUTICALS AND THEIR APPLICATIONS

Nutraceuticals list in Table 1.1. have positive effect on our health. But in most of the cases, the mechanism of the nutraceuticals was not established well i.e., most of them were used traditionally as medicines without proper scientific proof.

1.5.1. Alpha Carotene

This is found in Kiwi Fruit, Mango, Peach, Cantaloupe, Apricots, Carrots the richest source, Pumpkin second richest, Broccoli, Spinach, Kale, Brussels sprouts, and Sweet potato. It protects many forms of cancer: cervical, liver, pancreas, skin, lung, stomach, neuroblastoma and also protects against the development of cataracts. Carotene supplements derived from Palm Oil are the richest supplemental sources of Alpha carotene.

1.5.2. Anthocyanidins

These compounds are found in all berries and red. These compounds have antioxidant and anti-inflammatory. They strengthen connective tissue in the body and reduce capillary fragility i.e., bruising and help to prevent edema. They help in the prevention of cancer from spreading by strengthening the connective tissue and resist tumor invasiveness.
1.5.3. Astaxanthin:

This is found in some type of algae. It is a carotenoid. It has anti-inflammatory effects on nerve cells. It prevents bladder, colon and oral cancers in animals.

1.5.4. Catechin

This compound comes under the polyphenolic natural product. It is like all other polyphenolic natural product with a very good antioxidant component. It protects against many types of cancers, liver from alcohol damage and is useful in the treatment of hepatitis.
1.5.5. Curcumin

Curcumin, a major yellow pigment found in the rhizome of *cucuma longa*. It is a potent antioxidant, liver detoxifier and protector, gallstone prevention and cholesterol lowering compound. It suppresses the damage to liver cells caused by hepatitis C and stimulates glutathione by the liver. It is a potent cancer prevention and cancer treatment compound. It stimulates apoptosis of cancer cells. It assists in stopping all stages of cancer formation i.e., initiation, promotion and progression. Curcumin in preliminary studies suggests that it is likely to inhibit prostate, breast, skin, colon, stomach, and liver cancers and is suitable for use in conjunction with chemotherapy.

![Curcumin](image)

1.5.6. Ellagic Acid

This is found in raspberries, pomegranates, cranberries, apples, grapes, cherries, and strawberry. This helps to prevent various types of cancers in rodents, esophageal, lung, skin and helps to stimulate the manufacture of glutathione. Ellagic acid is also very good in cardiovascular protective.
1.5.7. Isoflavones\textsuperscript{13}

There are over 600 isoflavanoids. Daidzein, genistein, formononetin and biochanin A are known for their estrogenic properties. Isoflavones have received a lot of attention in the last decade in their support for menopause and in supporting conditions of overexpression of estrogen. They also have been used by men in supporting prostate health.

\begin{center}
\textbf{Isoflavones}
\end{center}

1.5.8. Lignans\textsuperscript{14}

Lignans found primarily in the outer husk of the flaxseed. These block estrogen receptors within the body, thereby inhibiting the toxic effects of excessive estrogens. They inhibit the development of breast cancer and inhibit the development of colon cancer and prostate cancer.
1.5.9. Limonene\textsuperscript{15}

This is found in the spongy white inner parts of citrus fruit i.e., orange peel, lemon peel, kumkuats and cranberry. This can dissolve gallstones. It inhibits the progression of established breast cancer and in animal studies with rodents, it prevented the development of pancreatic cancer and caused the regression of existing pancreatic cancer. In animal studies with breast cancer, it caused the complete regression of the majority of advanced rat breast cancers. Limonoids seem to work against cancer in three ways: prevent it from forming, slower the growth of existing cancer and kill the cancer cells.

![Limonene](image)

1.5.10. Lutein\textsuperscript{16}

This compound found in spinach, kale, broccoli, calendula marigold, egg yolk sweet potato, brussel sprouts, green beans, cayenne pepper and palm oil. It protects the eyes against the development of age-related Macular Degeneration. It helps in the prevention of breast, colon, prostate and lung cancers.

![Lutein](image)
1.5.11. Lycopene

This is found in many vegetables and fruits like tomato, grapefruit, watermelon, cayenne pepper, paprika, red grapes, the skin of red delicious apples, red papaya and apricots are good sources. Prostate and testicles are major storage areas for men. It prevents the body against prostate, bladder, breast, cervical, colon, endometrial, esophageal, leukemia, liver, lung, mouth, pancreatic and stomach cancers.

1.5.12. Omega 3 Fatty Acids

These are found in salmon and sardines and also in albacore tuna, flax seed. Omega 3 plays a critical role in the brain and in cell membrane fluidity. They are potent controllers of the inflammatory processes.

1.5.13. Quercetin

This is found in red onions, apples and the skins of russet potatoes, red wine, green tea, black tea, apples, grapes, pears, kiwi, califlower, spinach, broccoli, kale, cabbage,
cayenne, green beans, okra, fennel and squash. It helps to prevent cataracts. It has significant antitumor activity against various form of cancer i.e., brain, breast, colon, leukemia, lung, ovarian, squamous cell carcinoma and it stimulates apoptosis cellular death in cancer cells. It is best known for its anti-inflammatory, anti-allergy and for allergic asthma. It is the best single nutritional strategy for the treatment of any kind of allergy. It appears to protect brain cells against oxidative stress. It can prevent infections caused by viruses. It has also antioxidant, anti-cancer, anti-inflammatory and anti-allergy properties also.

![Quercetin](image)

**1.5.14. Resveratrol**

It is found in red wine, dark grape juice, dark muscadines, raisins and whole seeded dark grapes the skin and the seeds, cranberries, mulberries and peanuts. It helps in the prevention of atherosclerosis and inhibits abnormal blood clotting. It lowers total serum cholesterol increasing HDL and prevents the oxidation of LDL cholesterol. It may be one of the most potent Cox-2 inhibiting anti-inflammatory substances found in nature. It has major cancer inhibiting effects. It is also important in helping fight leukemia, colon cancer, skin cancer, prostate cancer, melanoma and thyroid cancer where it stimulates apoptosis.
1.5.15. Rutin\textsuperscript{21}

It is found in bee pollen, red wine, buckwheat, yerba mate, garlic, fennel and hawthorne. It strengthens the blood vessels and prevents bruising. It is useful in treating hemorrhoids. It has been shown helpful for people with Glaucoma by strengthening the connective tissue of the eye and is useful for allergies and inflammation like quercetin though not as powerful.

1.5.16. Theophiline\textsuperscript{22}

This is found in green tea. It is very helpful for the treatment of asthma. It has anticancer activity also.
1.6. TURMERIC AND CURCUMIN

1.6.1. Curcuma longa

Turmeric, a source of vital nutraceutical curcumin is a rhizomatous herbaceous perennial plant of the ginger family, Zingiberaceae. Its origin is tropical South Asia. The rhizome of this plant is the most useful part of the plant for culinary and medicinal purposes. Turmeric is used as a dietary spice, coloring agent in foods and textiles, and a treatment for a wide variety of ailments. The most active component of turmeric is curcumin, which makes up 2 to 5% of the spice\textsuperscript{23}. The characteristic yellow color of turmeric is due to the curcuminoids\textsuperscript{24}. The world's largest producer and most important trading center of turmeric in Asia is Erode, TamilNadu.
Taxonomy

Kingdom : Plantae
Phylum   : Magnoliophyta
Class    : Liliopsida
Order    : Zingiberales
Family   : Zingiberaceae
Genus    : Curcuma
Species  : *Curcuma longa*

**Fig. 1.2.** Turmeric plant – Turmeric Rhizome - Turmeric Powder
1.6.2. Chemical composition of turmeric

Turmeric contains protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%) and moisture (13.1%). The essential oil (5.8%) obtained by steam distillation of rhizomes has a-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%)\(^25\). Curcumin (diferuloylmethane) (3 – 4%) is responsible for the yellow colour, and comprises curcumin (94%), demethoxycurcumin (6%) and bisdemethoxycurcumin (0.3%)\(^26\).

Curcumin was first isolated in 1815 and its chemical structure was determined by Roughley and Whiting\(^27\) in 1973. It has a melting point at 183\(^o\)C with molecular formula of \(C_{21}H_{20}O_6\), and its molecular weight is 368.37. It forms a reddish - brown salt with alkali and is soluble in ethanol, methanol, dichloromethane, ethylacetate, chloroform acetic acid and with various solvents.

1.6.3. Biological activity of turmeric and its compounds

The turmeric and its various compounds possess a variety of biological activities. Fifty percent ethanolic extract of \textit{curcuma longa} shows hypolipemic action\(^28\) in rats and also possess antitumour activity\(^29\). Turmeric powder has healing effect on both aseptic and septic wounds in rats and rabbits\(^30\). It also shows chemoprotection in experimental forestomach and oral cancer models of mice. Alcoholic extract and turmeric shows antibacterial activity\(^31\). The crude ether and chloroform extracts of \textit{curcuma longa} stem are also reported to have antifungal activity\(^32\). The extracts of the rhizomes of \textit{curcuma longa} have been in use from the vedic ages\(^33\).
Curcumin, a secondary metabolite and the main yellow compound of *cucuma longa* rhizome which is the main component of turmeric powder is widely used as a traditional medicine in widespread in several parts of Asia\(^3\). Due to its various biological activities, curcumin is one of the compounds mostly modified and numerous numbers of analogues were made towards the optimization of various biological activities. The pubmed citations on curcumin from 1990 to 2010 say clearly the importance of curcumin (Fig. 1.3. and 1.4.).

**Fig. 1.3.** Pubmed citations on curcumin from 1990-2010
1.7. PHARMACOLOGICAL ACTION OF CURCUMIN

1.7.1. Antioxidant effect

An antioxidant is a molecule capable of inhibiting the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. The antioxidant activity of curcumin was reported as early as 1975. It acts as a scavenger of oxygen free radicals. It protects haemoglobin from oxidation. In vitro, curcumin can significantly inhibit the generation of ROS. Curcumin exerts powerful
inhibitory effect against H$_2$O$_2$ induced damage in human keratinocytes and fibroblasts$^{38}$ and in NG 108-15 cells$^{39}$. It also decreases lipid peroxidation in rat liver microsomes, erythrocyte membranes and brain homogenates$^{40}$.

1.7.2. Anti-inflammatory activity

Anti-inflammatory refers to the property of a substance or treatment that reduces inflammation. Curcumin is effective against carrageenin-induced oedema in rats and mice$^{41,42,43}$. The antirheumatic activity of curcumin has been established in patients who showed significant improvement of symptoms after administration of curcumin$^{44}$. Curcumin offers antiinflammatory effect through inhibition of NFκβ activation$^{45}$. Curcumin has been shown to reduce the TNF-α-induced expression of the tissue factor gene in bovine aortic-endothelial cells by repressing activation of both AP-1 and NFκβ$^{46}$. The anti-inflammatory role of curcumin is mediated through downregulation of cyclooxygenase-2 and inducible nitric oxide synthetase through suppression of NFκβ activation$^{47}$. Curcumin also enhances wound-healing in diabetic rats and mice$^{48}$.

1.7.3. Anticarcinogenic effect

Curcumin is a potent anticarcinogenic compound through various mechanisms. Colon carcinoma is prevented by curcumin through arrest of cell-cycle progression independent of inhibition of prostaglandin synthesis$^{49}$. Curcumin suppresses human breast carcinoma through multiple pathways. Its antiproliferative effect is estrogen dependent in ER-positive MCF-7 cells. Curcumin also suppresses tumour growth through various
pathways. Nitric oxide and its derivatives play a major role in tumour promotion. Curcumin inhibits iNOS and COX-2 production\textsuperscript{50} by suppression of NF\textgreek{k}B activation\textsuperscript{47}. Recently, in Jurkat cells, curcumin has been shown to prevent glutathione depletion, thus protecting cells from caspase-3 activation and oligonucleosomal DNA fragmentation\textsuperscript{51} in curcumin exerts both pro and antimutagenic effects. At 100 and 200 mg / kg body weight doses, curcumin has been shown to reduce the number of aberrant cells in cyclophosphamide-induced chromosomal aberration in Wistar rats\textsuperscript{52}. Turmeric also prevents mutation in urethane models\textsuperscript{53}.

1.7.4. Anticoagulant activity

Curcumin shows anticoagulant activity by inhibiting collagen and adrenaline-induced platelet aggregation \textit{in vitro} as well as \textit{in vivo} in rat\textsuperscript{54}.

1.7. 5. Antifertility activity

Curcumin inhibits 5\alpha-reductase, which converts testosterone to 5\alpha-dihydrotestosterone, thereby inhibiting the growth of flank organs in hamster\textsuperscript{55}. Curcumin also inhibits human sperm motility and has the potential for the development of a novel intravaginal contraceptive\textsuperscript{56}. Petroleum ether and aqueous extracts of turmeric rhizomes show 100\% antifertility effect in rats when fed orally\textsuperscript{57}. Implantation is completely inhibited by these extracts\textsuperscript{58}.
1.7.6. Antidiabetic effect

Curcumin prevents galactose-induced cataract formation at very low doses\(^5^9\). Both turmeric and curcumin decrease blood sugar level in alloxan-induced diabetes in rat\(^6^0\). Curcumin also decreases advanced glycation end products induced complications in diabetes mellitus\(^6^1\).

1.7.7. Antibacterial activity

It has been observed that both curcumin and the oil fraction suppress the growth of several bacteria like *Streptococcus*, *Staphylococcus*, *Lactobacillus*, etc\(^6^2\). The aqueous extract of turmeric rhizomes has antibacterial effects\(^6^3\). Turmeric and curcumin possess moderate activities against *E.Coli*, *S.aureus*, *V.cholera*, *S.typhi* and *P.aeuroginosa*\(^6^4,6^5\).

1.7.8. Antifungal effect

Ether, ethanol, chloroform extracts and oil of *curcuma longa* have antifungal effects\(^6^6,6^7\). Turmeric oil is also active against *Aspergillus flavus*, *A. parasiticus*, *Fusarium moniliforme* and *Penicillium digitatum*\(^6^8\). Curcumin has moderate antifungal activity against *Cardiac albicans*\(^6^4\).

1.7.9. Antiprotizoaan activity

The ethanol extract of the rhizomes has anti-Entamoeba histolytica activity. Curcumin has anti-Leishmania activity *in vitro*\(^6^9\). Several synthetic derivatives of curcumin
have anti-Leishmania amazonensis effect\textsuperscript{70}. Anti-Plasmodium falciparum and anti-Leishmania are the major effects of curcumin have also been reported\textsuperscript{71}.

1.7. 10. Antiviral effect
Curcumin shows anti-HIV activity by inhibiting the HIV-1 integrase needed for viral replication\textsuperscript{72}. It inhibits EBV\textsuperscript{73}.

1.7. 11. Antifibrotic effect
Curcumin suppresses bleomycin-induced pulmonary fibrosis in rats\textsuperscript{74}. Oral administration of curcumin at 300 mg/kg dose inhibits bleomycin-induced increase in total cell counts and biomarkers of inflammatory responses. It also suppresses bleomycin-induced alveolar macrophage-production of TNF-\textit{\alpha}, superoxide and nitric oxide. Thus curcumin acts as a potent antiinflammatory and antifibrotic agent.

1.7.12. Antivenom effect
Ar-turmerone, isolated from \textit{curcuma longa}, neutralizes both haemorrhagic activity of Bothrops venom and 70\% lethal effect of Crotalus venom in mice\textsuperscript{75}. It acts as an enzymatic inhibitor of venom enzymes with proteolytic activities\textsuperscript{76}.

1.8. PHARMACOKINETIC STUDIES ON CURCUMIN
Curcumin, when given orally or intraperitoneally to rats, is mostly egested in the faeces and only a little in the urine\textsuperscript{77,78}. Only traces of curcumin are found in the blood from the heart, liver and kidney. Curcumin, when it is added to the isolated hepatocytes, is
quickly metabolized and the major biliary metabolites are glucuronides of tetrahydrocurcumin and hexahydrocurcumin\textsuperscript{79,80}. After metabolism in the liver, curcumin is mainly excreted through bile.

1.8.1. Clinical studies and medicinal applications of turmeric and curcumin

Curcumin is used for the treatment of biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis in traditional Indian medicine\textsuperscript{81}. Turmeric powder is used to treat wounds, bruises, inflamed joints and sprains\textsuperscript{82}. Data are also available showing that the powder, when applied as capsules to patients with respiratory disease, gives relief from symptoms like dyspnoea, cough and sputum\textsuperscript{83}. In patients undergoing surgery, oral application of curcumin reduces post-operative inflammation\textsuperscript{84}. Recently, curcumin has been formulated as slow-release biodegradable microspheres for the treatment of inflammation in arthritic rats\textsuperscript{85}.

1.8.2. Safety evaluation with turmeric and curcumin

The average intake of turmeric by Asians varies from 0.5 to 1.5 g/day/person, which produces no toxic symptoms\textsuperscript{86}. Male and female Wistar rats, guinea pigs and monkeys were fed with turmeric at much higher doses (2.5 g/kg body weight) than normally consumed by humans. No changes were observed in the appearance and weight of kidney, liver and heart\textsuperscript{80}. Also, no pathological or behavioural abnormalities were noticed and no mortality was observed.
1.9. CURCUMIN DERIVATIVES, ANALOGUES AND VARIOUS BIOLOGICAL ACTIVITIES

Curcumin has the following possibilities for structural alteration as shown in Fig. 1.5. Alterations of structure at all these molecular architectural sites are attempted.

![Curcumin and possible structural modification](image)

**Fig. 1.5.** Curcumin and possible structural modification

The modification of the basic structure of curcumin can be classified into two categories. These are:

1. Curcumin derivatives
2. Curcumin analogues

1.10. CURCUMIN DERIVATIVES

Compounds that derived from curcumin, by utilizing the functional groups such as phenol, 1,3-diketone, active methylene, alkenyl double bond are classified as curcumin derivatives. The curcumin derivatives are further divided in to two groups. They are

1. Curcumin derivatives by organic reaction
2. Curcumin derivatives by complex formation
1.10.1. Curcumin derivatives by organic reaction

The curcumin derivatives are generally synthesized by derivatization, starting from curcumin. The phenolic hydroxy group is acylated, alkylated, glycosylated, and amino acylated\(^{87-101}\). The methoxy group is demethylated to hydroxy groups\(^{102}\). The active methylene group is acylated or alkylated or substituted by an arylidene group\(^ {103}\). The hydrogenation of the C7 linker double bonds and the carbonyl groups affords the simplest of the analogues, such as dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin and octahydrocurcumin, which are obtained by the reduction of curcumin\(^ {104-107}\). The central 1,3-diketone is converted to pyrazole, oxazole by reacting the curcumin with hydrazine, hydroxylamine respectively\(^ {108-111}\).

Fig. 1.6. Curcumin derivatives
The monosemicarbazone\textsuperscript{112}, bisthiosemicarbazone\textsuperscript{113} and an ethylene diamine adduct\textsuperscript{114} of curcumin have also been synthesised. The reduction of alkene bonds followed by the masking of 1,3-diketone allows several heterocyclic compounds to synthesis\textsuperscript{115}. The piperidones also synthesised by converting the alkene and keto group with amine under microwave conditions\textsuperscript{116}.

### 1.10.2. Curcumin derivatives by complex formation

Metal complexes of curcumin are synthesized by the reaction of curcumin with a metal salt. Boron has long been known to form a complex with curcumin\textsuperscript{117}. The complex resulting from combination of a molecule of curcumin, oxalic acid, and a boron atom, sourced from boric oxide or acid, is known as rubrocurcumin. The complexation of two curcumin molecules with a boron atom affords rosocyanin. Complexes of copper\textsuperscript{118-120}, iron, manganese\textsuperscript{121-125}, palladium\textsuperscript{126}, vanadyl\textsuperscript{127}, gallium, and indium\textsuperscript{128,129} have been reported.

### 1.11. CURCUMIN ANALOGUES

Curcumin analogues are synthesised from smaller synthons like araldehydes and acetylacetone, cyclic ketones like piperidone, cyclohexanone etc. Several approaches like converting the central 1,3-diketone into phenyl, heteroaryl, aliphatic chains, extending the chain length, etc., in view of finding interesting biological properties have been attempted. The five carbon analogues are synthesized from piperidone, acetone with aldehydes. The seven carbon analogues are synthesized from various synths like acetyl acetone, 2-
acetylcycloakanones. The extended chain lengths like C9, C11 or longer chains also attempted in view of the increased biological activity. The total numbers of such analogues now synthesized are too many to depict conveniently$^{130-164}$. 

![Six Carbon linker](image)

![Five Carbone linker](image)
1.12. BIOLOGICAL ACTIVITIES OF CURCUMIN ANALOGUES AND DERIVATIVES

Most of the curcumin based compounds were screened for the antioxidant, anti-inflammatory, anticancer activities. The anti-inflammatory behaviour of curcumin is improved a lot by its analogues. The hydrazinocurcumin possess more antiangiogenic activity than curcumin itself. 2,6-bis(2-fluorobenzylidene) piperidine (EF24) shows more antiangiogenesis than curcumin. Curcumin analogues possess more antioxidant activity due to the hydroxyl and central beta diketo groups scavenging activity of free radicals. The detailed discussion of antioxidant activity of curcumin derivatives is discussed in Chapter 4.
1.13. SCOPE AND OBJECTIVE

The main scope and objective of the present study is:

i) To synthesize the 3,5-diarylidene-4-piperidone and corresponding sulfonamide, carboxamide derivatives. To characterize the compound with the assistance of $^1$H NMR, $^{13}$C NMR and LCMS data

ii) To evaluate the 3,5-diarylidene-4-piperidone and corresponding sulfonamide, carboxamide derivatives against the gram positive and gram negative bacterias

iii) To establish SAR analysis and improve the biological activities by bioisostere concept

iv) To analyse the turmeric phytochemically, to isolate and characterize the curcuminoids

v) To synthesize the heteroarylhydrazinocurcumin and arylhydrazinocurcumin from curcumin with the help of microwave reaction condition to achieve good yield as well as reduced reaction time. To characterize the compound with the assistance of $^1$H NMR, $^{13}$C NMR and LCMS data

vi) To evaluate the novel heteroarylhydrazinocurcumins against in vivo antioxidant assays considering curcumin as standard


7. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of Cook N. R.; Albert, C. M.; Gaziano, J. M. Cardiovascular events in women:


43. Srimal, R. C.; Dhawan, B. N. In Development of Unani drugs from Herbal Sources and the Role of Elements in their Mechanism of Action (ed. Arora, B. B.), Hamdard National Foundation Monograph, New Delhi, **1985**, 201-212.


80. Holder, G. M.; Plummer, J. L.; Ryan, A. J. The metabolism and excretion of curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) in the rat. *Xenobiotica*, 1978, 8, 761–768.


curcumin and its analogues (Congeners) made by man and Mother Nature. *Biochem. Pharm.* **2008**, *76*, 1590 – 1611


