CHAPTER-2

LITERATURE REVIEW

LITERATURE REVIEW

2.1. *Curcuma longa*

Curcuma longa is a rhizomatous herbaceous perennial plant of the Zingiberaceae family. It is now widely cultivated and diversely processed in India, China, and many other countries for obtaining dried rhizomes and other products from them for culinary as well as medicinal purposes. In India, it is popularly known as "*Haldi"*. In Malaysia, Indonesia and India, turmeric has been well studied due to its economic and medicinal importance. In Ayurveda, turmeric has been used internally as a tonic, analgesic and blood purifier and externally in the prevention and treatment of skin diseases [H. Hatcher et al., 2008]. Traditional Indian medicine claims the use of its powder against biliary disorders, anorexia, cough, coryza, diabetic wounds, rheumatism, and sinusitis [H.P.T. Ammon et al., 1992]. It is also used as colouring, flavouring and food presetvative. *Curcuma longa* mainly contains the curcuminoids (curcumin, demethoxycurcumin and bisdemethoxycurcumin), essential oil (turmerones and zingiberine) and turmerin (water soluble peptide). Most of the pharmacological activities of *Curcuma longa* are attributed to curcumin and its other curcuminoids. Curcumin is hydrophobic polyphenol, also known as diferuloylmethane that exhibits keto-enol tautomerism, having a predominant keto form in neutral and acidic solutions and a stable enol form in alkaline media. Due to its extra-ordinary molecular structure it shows strong anti-oxidative, as well as anti-inflammatory properties. It is insoluble in water, but is readily soluble in organic solvents such as dimethylsulfoxide, acetone, and ethanol. Currently it is phytochemically and pharmacologically one of the most extensive studied edible plant derived products of medicinal interest.

2.1.1. Vernacular names

Hindi: Haldi

Sanskrit: Ameshta

Chinese: Wat gam

English: Indian saffron

Romanian: Curcuma

Japanese: Ukon

2.1.2. Other names: Manjal, Haridra, Gurkemeje, Toormer, Kolkuma, Acafrao da India, Hint safrani, Gurkmeja, Gaser, Romiet, Kunyit, Wat gam, Harilik kurkuma, Manjano, Halodhi.

2.1.3. Taxonomy

Kingdom: Plantae

Subkingdom: Tracheobionta

Superdivision: Spermatophyta

Division: Magnoliophyta

Subclass: Zingiberidae

Order: Zingiberales

Family: Zingiberaceae

Genus: Curcuma

Species: Longa

Scientific name: *Curcuma longa*

Figure 2.1: *Curcuma longa* L. Plant

2.1.4. Morphological outline

- The plant is a rhizomatous herbaceous and perennial, with 60-90 cm high and a short stem tufted leaf.
- Its flowers are yellow in colour, 10-15 cm in length and grouped together in dense spikes.
- No fruits are found in this plant.
- Rhizome measures 2.5-7.0 cm (in length), and 2.5 cm (in diameter) with small tuber branching.
- The rhizome is yellowish-brown with a dull orange interior that looks bright yellow when get powdered.

2.1.5. Botanical description

Curcuma longa L. is herbaceous plant that reaches up to 1 m (3 ft 3 in) in hieght. It is also called as rhizamatous plant because to contain highly branched, cylindrical and aromatic rhizomes. The leaves are alternate and arranged in two rows. They are divided into leaf sheath, petiole, and leaf blade. The petiole is 50 to 115 cm long, although leaf blades are usually 76 to 115 cm long and rarely up to 230 cm in length. They have a width of 38 to 45 cm and are oblong to elliptical in shape with narrowing tip. It is propagated by cuttings from

the root, which when dry its curved cylindrical or oblong tubers 2 or 3 inches in length, pointed or tapering at one end, yellowish with transverse parallel rings, dense, solid, forming a lemon yellow powder. It has aromatic fragrant odour and slightly acrid or bitter taste, like ginger, exciting warmth in the mouth and coloring the saliva. It yields its properties to water or alcohol.Turmeric can be cultivated in diverse tropical conditions, to upto 1,500-1,600 meters from the sea level, with temperatures varying from 30±10 ºC, and rainfall above 1600 mm. It is a nine-month crop sown in July and harvested in April. Turmeric thrives in well-drained, fertile, sandy and black, red loams, rich in humus and uniform in texture. The crops are ready for harvest in seven to nine months depending upon the time of sowing. Harvested rhizomes are cleaned of mud and other extraneous matter adhering to them. The rhizomes are boiled in water, which are spread out on a floor and allowed to dry in the sun for about 15-20 days. After uniform dryng rhizomes are converted into the powder form for its commercial, domestic medicinal and dietary use. India is the largest consumer, producer and exporter of turmeric in the all over world. Turmeric is grown in as many as 25 states of India with Tamilnadu, Karnataka, Andhra Pradesh and Odisha being the leading producers. India has nearly 1.73 lakh hectares under turmeric cultivation with a total production of 8.55 lakh tones during the year. Currently, India is the major producer and consumer of turmeric. China is second largest supplier of the turmeric and it is followed by a number of the countries in the Indian sub-continent, Southeast Asia, the Caribbean and Latin America. India produces about 80% of world turmeric and exported about 60% of its total production. Some of the important varieties of turmeric exported from India such as Rajapuri, Madras, and Allepy finger turmeric.

2.1.6. Phytochemistry

Turmeric has hundreds of molecular constituents, each with a variety of biological activities. For instance, there are at least 20 molecules that are antibiotic, 12 are anti-inflammatory, 14 are known for cancer preventives, 12 that are anti-tumor, and there are at least 10 different anti-oxidants. To date, at least 235 compounds, primarily phenolic compounds and terpenoids have been identified, including diarylheptanoids, diarylpentanoids, monoterpenes, sesquiterpenes, diterpenes, triterpenoids, alkaloid, sterols and fatty acid etc. Curcuminoids belong to the group of diarylheptanoids (or diphenylheptanoids) having an aryl-C7-aryl skeleton. These yellow pigments are usually used as food coloring agents and they are the main active compounds of turmeric viz. curcumin, demethoxycurcumin and bisdemethoxycurcumin [E. Pfeiffer et al., 2003]. Usually, these polyphenols are present in 3-15 % of turmeric rhizomes as the principal compound. The volatile oils from leaves and flowers of *Curcuma longa* were usually dominated by monoterpenes, particularly *p*-cymene, *β*-phellandrene, terpinolene, cineole and myrcene while the major part of the oil from roots and rhizomes contained sesquiterpenes [B. Chempakam and V.A. Parthasarathy 2008; B.O. Oguntimein et al., 1990]. Dried turmeric rhizomes usually yield 1.5 to 5% essential oils which are dominated by sesquiterpenes and are responsible for its aromatic taste and smell. *Ar*-turmerone, *α*-turmerone and *β*-turmerone are major ketonic sesquiterpenes of essential oils, and these compounds may account for at least 40% of essential oils of turmeric rhizomes. Structures of some quantitatively major diarylheptanoids and sesquiterpenes commonly encountered in such extracts are shown in **Figure 2.2.** Other than major components diterpenes, triterpenoids, steroids and long chain fatty acids were also identified in turmeric [L.A. Usman et al., 2009; X. Ma and D.R. Gang 2006; J.J. Chen et al., 2010]

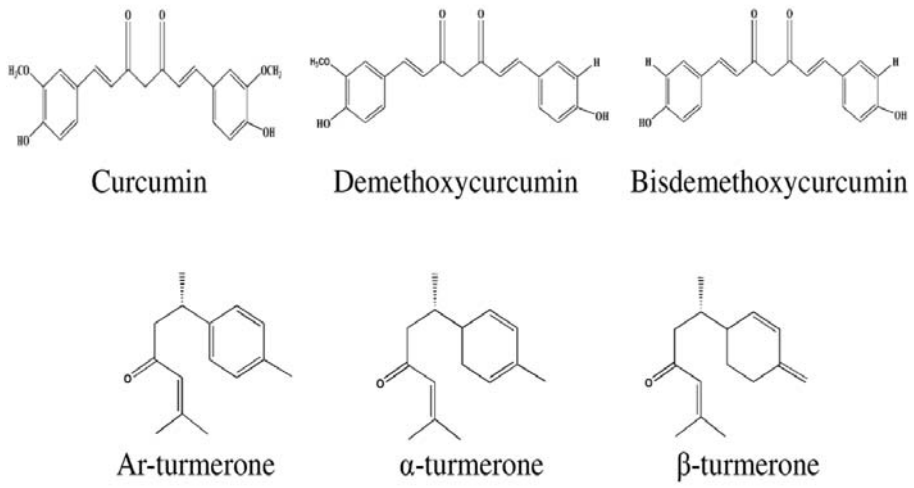

Figure 2.2: Major phytochemical constituents from *Curcuma longa*

2.1.7. Pharmacology

Available clinical and preclinical information on curcuminoids and diverse types of *Curcuma longa* extracts strongly suggests that most probably curcumin is the quantitatively major, but not the only, bioactive constituent of the plant. Several studies have confirmed that curcumin functions as an antioxidant, anti-inflammatory, and anti-atherosclerotic as well as inhibits scarring, cataract, and gallstone formation. It also promotes wound healing and muscle regeneration, prevents liver injury and kidney toxicity and exerts other medicinal benefits against psoriasis, multiple sclerosis, cardiovascular disease, lung fibrosis, diabetes, arthritis and inflammatory bowel disease [B. Aggarwal et al., 2003; R. Sharma et al., 2005; B. Aggarwal and S. Shishodia 2006; J. S. Jurenka 2009]. Recently, curcumin has garnered interest as a potential anticancer agent, for both chemo preventative and chemotherapeutic purposes. In *vitro* cell culture and *in vivo* animal studies have suggested that curcumin may be able to treat numerous types of cancer, including breast cancer, kidney cancer, liver cancer; colon cancer and leukemia [K. Mehta et al., 1997; R. Hanif et al., 1997]. Several

recent studies have highlighted the potential use of curcumin and other curcuminoids as an antimicrobial and antiviral agent. In recent years, there has been a growing interest in the potential pharmacological effects (particularly protective effects) of curcumin in the cardiovascular system [G. Srivastava and J. Mehta 2009]. Much attention has also been placed on the neurotherapeutic and neuroprotective potential of curcumin in recent years [S. Kulkarni and A. Dhir, 2010]. A Chinese study investigated the potential of curcumin as a therapeutic agent in Alzheimer's disease *in vitro* and *in vivo* [X.Y. Qin et al., 2010; F. Yang et al., 2005]. Because of the increasing evidence that the pathogenesis of type 2 diabetes mellitus and obesity is connected to inflammation, curcumin has emerged as a potential drug of interest for diabetic and obesity pharmacology [B. Aggarwal, 2010; A. Shehzad et al., 2011]. An *in vivo* study in rats demonstrated that pretreatment with curcumin exerted a potent protective effect on the lungs following cardiopulmonary bypass. An another recent study demonstrated a possible mechanism for the therapeutic use of curcumin as an agent for the treatment of alimentary disorders such as diarrhea, abdominal cramps, and irritable bowel syndrome [A. Kumar et al., 2010]. In one of the first studies investigating the effect of curcumin on the reproductive system, it was discovered that curcumin dose-dependently inhibited the forward motility of both murine and human sperm, the capacitation, acrosome reaction, and murine fertilization *in vitro* [Y. Quan and Q. Liu, 2016]. The above mentioned research studies, as well as many more not described here, suggest that the potential clinical application of curcumin is extremely vast, owing to its diverse and potent array of pharmacological effects in almost all of the major organ systems of the human body. Some many other therapeutically interesting pharmacological activities reported for the *Curcuma longa* extract and its secondary bioactive metabolite curcumin are summarized in **Table 2.1**

& 2.2. These effects are supported by an equally vast amount of molecular targets and mechanisms of action shown by the compound in a large host of cell types both *in vitro* and *in vivo*. It is best therapeutic option for prevention and therapy of numerous human pathological conditions, particularly inflammatory-based processes and perhaps most importantly, cancer. Many of its formulations with various therapeutic indications are now being in market; some of them are mentioned in **Table 2.3 & 2.4**. It has been said by Hippocrates that, "Let food be thy medicine and medicine be thy food." Curcumin and *Curcuma longa* extract may indeed be the medicine and the food that the world has been looking for since long time.

2.1.8. Bioavailability

Curcumin has received extensive attention over the past few years, which is mostly due to its diverse biological activities. Numerous reports have shown that, even with high doses of curcumin, the levels of curcumin as well as its *in vivo* metabolites are extremely low in serum and tissues after a short period of time [P. Anand et al., 2007; R.E. Carroll et al., 2011; N. Dhillon et al., 2008; R.A. Sharma et al., 2001]. Numerous preclinical and clinical studies indicated the great potential of curcumin in treating these diseases, but the application of curcumin in the therapeutic treatment was hindered by its poor systemic bioavailability. In addition to poor solubility, curcumin is unstable in aqueous solution and undergoes rapid hydrolysis followed by molecular fragmentation at physiological pH [Y.J. Wang et al., 1997; J.K. Lin et al., 2000], which has been considered another potential limitation for its therapeutic use. Wang et al., 1997 found that 90% of curcuminoids degraded within 30 min in phosphate buffer at pH 7.4 into various products, identified as ferulic aldehyde, ferulic acid, feruloyl methane and vanillin. Although the presence of the degraded products *in vivo*

has not attracted wide attention and these products have not been even identified in most of the studies. A preliminary study reported the presence of dihydroferulic acid and ferulic acid in the bile after oral curcumin administration in rats [G.M. Holder et al., 1978] indicating that the degradation products of curcumin are present *in vivo* and thus may be associated with its biological activity [H. Hatcher et al., 2008]. The antioxidant activity of curcumin has been proposed to be associated with most of its pharmacological effects, and another study revealed that curcumin-derived radical reaction products viz. ferulic acid and vanillin also possess curcumin like antioxidant activity [T. Masuda et al., 1999]. Curcumin and its metabolites products in combating many diseases and on the basis of preferential role of the degradation products in inhibiting enzymes, we propose that the bioactive degraded products contribute to the observed pharmacological effects of consuming curcumin. Curcumin and other metabolites of *Curcuma longa* extract always have poor bioavailability even then its various pharmacological activities have been widely recognized. Many studies revealed that curcumin and its degradation products possess similar pharmacological profiles in anti-cancer, anti-inflammation and antimicrobial activities, which could conclude that the bioactive degradation products of curcumin are important contributors to its pharmacological activities [M. Heger et al., 2013; L. Shen and H.F. Ji, 2012; H.F. Ji and L. Shen 2014]. A recent *in vivo* study showed that the degradation products above mentioned are the major human metabolites produces after curcumin consumption and their levels are much higher than those of curcuminoids [P. Vitaglione et al., 2012]. Several experimental and theoretical findings suggested that the degradation products should play important roles in executing the biological and pharmacological activities of curcumin [L. Shen et al., 2016].

2.1.9. Safety

In more recent preclinical studies of curcumin, no toxicity has been observed from 2% dietary curcumin (approximately 1.2 g/kg BW) administered to rats for 14 days [R.A. Sharma et al., 2001] or from 0.2% dietary curcumin (approximately 300 mg/kg BW) administered to mice for 14 weeks [S. Perkins et al., 2002]. Some clinical reports suggest that dietary consumption of *Curcuma longa* up to 1.5 g per person per day, equating to a maximum of 150 mg/day of curcumin, are not associated with any adverse effects in humans [D. Eigner and D. Sholz 1999]. An another study revealed that administration of 1.2-2.1 g of oral curcumin daily to patients with rheumatoid arthritis for 2-6 weeks did not show any adverse effects [S.D. Deodhar et al., 1980]. In patients with advanced colorectal cancer treated in the curcumin was well tolerated at all dose levels up to 3.6 g daily for up to 4 months [R.A. Sharma et al., 2004]. Therfore, on the basis of preclinical and clinical reports it is reconfirmed that *Curcuma longa* and curcumin are safe therapeutic agents even at their high and repeated high doses.

Table 2.1: Reported preclinical observations made with diverse types of *Curcuma longa* extracts.

S. No.	Type of extract	Pharmacological activity	Dose, duration and route of administration	References
1.	Hexane extract	Antioxidant	100-500 mg/kg, 30 days, p.o. 400 µg/ml *in vitro*	V.B. Liju et al., 2011
2.	Hexane extract	Antiinflamatory	100-1000 mg/kg, 5 days, i.p.	V.B. Liju et al., 2011
3.	Hexane extract	Antinoception	100-1000 mg/kg, single dose, p.o.	V.B. Liju et al., 2011
4.	Ethanolic extract	Anti-depression	50-100 mg/kg, 21 days, p.o. 140-560 mg/kg, 14 days, p.o.	X. Xia et al., 2007 Z.F. Yu et al., 2002
5.	Ethanolic extract	Atherosclerosis	3.2 mg/kg, 7 weeks, p.o.	M.C. Ramirez-Tortosa et al., 1999
6.	Ethanolic extract	Anticancer	1 µl/ml *in vitro*	J.H. Naama et al., 2010
7.	Ethanolic extract	Diabetes	0.2-1.0 g /100 g, 4 weeks, p.o.	M. Kuroda et al., 2005
8.	Aqueous extract	Hepatotoxicity	50 mg/ml, 14 days, p.o.	K.B. Soni et al., 1992

9.	Aqueous extract	Myocardial apoptosis	100 mg/kg, 30 days, p.o.	I. Mohanty et al., 2006
10.	Ethanolic extract	Ulcers	500 mg/kg, single dose, p.o.	S. Rafatullah et al., 1990
11.	Methenolic extract	Rheumatoid Arthritis	4 mg/kg, 4 days, p.o.	J.L. Funk et al.,2006
12.	Ehyl acetate extract	Antimicrobial	4 mg /ml *in vitro*	K.J. Kim et al., 2003
13.	Ethanolic extract	Wound healing	5% w/w, 15 days, topical	S.K. Purohit et al., 2013
14.	Ethanolic extract	Cardiotoxicity	200 mg/kg, 9 days, p.o	E.M. El-Sayed et al., 2011
15.	Hexane extract	Antifungal	1000 mg/L *in vitro*	M.K. Kim et al., 2003
16.	Methanolic extract	Antiobesity	20 µg/mL *in vitro*	J. Park et al., 2013
17.	Aqueous extract	Myocardial injury	100 mg/kg, 30 days, p.o.	I. Mohantya et al., 2004
18.	Aqueous extract	Antiviral	500 mg/L *in vitro,* 9 days	H.J. Kim et al., 2009
19.	Hexane extract	Cytotoxic	68 µg /ml *in vitro*	J. Ranjbari et al., 2014

Table 2.2: Some reported pharmacological activities of Curcumin

S. No.	Pharmacological activity	Dose, duration and route of administration	References
1.	Wound healing	40 mg/kg, 11days, i.p.	G.S. Sidhu et al., 1998
2.	Epilepsy	300 mg/kg, 30 days, p.o.	J. Mehla et al., 2010
3.	Parkinson disease	200 mg/kg, 24 days, p.o.	X.X. Du et al., 2012
4.	Alziemers disease	20 µM/L *in vitro*	S.S. Ambegaokar et al., 2003
5.	Cerebral injury	1-2 mg/kg, single dose i.v.	J. Jiang et al., 2007
6.	Arthritis	50 mg/kg, 15 days, i.p.	G. Huang et al., 2013
7.	Asthma	5 mg/kg, single dose, i.n.	Subhashini et al., 2013
8.	Psoriasis	1% gel, 10 days, topical	J. Sun, et al., 2013
9.	Lung fibrosis	200 mg/kg, 28 days, p.o.	D. Zhang et al., 2011
10.	Nephrotoxicity	60 mg/kg, 5days, p.o.	A. Kuhad et al., 2007
11.	Cataract	75 mg/kg, 14 days, p.o.	S. Awasthi et al., 1996
12.	Anti HIV	1.75µM *in vitro*	U. Gandapu et al., 2011
13.	Cardiotoxicity	200-400 mg/kg, 4 days, p.o.	S.R. Naik et al., 2011
14.	Neuroprotective	100 mg, 28 days, p.o	R.S. Yadav et al., 2011
15.	Memory	40 mg / kg, 3 days, i.p	S.Y. Yu et al., 2013
16.	Intestinal ischemia	200 mg / kg, 20 days, i.p	N. Okudan et al., 2013
17.	Pancreatitis	50 mg/kg, 6 days, i.p.	W.G. Yu et al., 2011
18.	Antioxidant	100-200 mg/kg, 4days, p.o.	S.R. Naik et al., 2011

19.	Ulcerative colitis	50 mg/kg, 10 days, p.o.	J.S. Jurenka, 2009
20.	Hepatotoxicity	100-200 mg/kg, 4 days, p.o.	S.R. Naik et al., 2011
21.	Mutagenicity	1000 µg *in vitro*	P. Smerak et al., 2006
22.	Ulcers	20-80 mg/kg, 10 days, p.o.	M. Sirima et al., 2006
23.	Anti-depression	10 mg/kg, 3 weeks, p.o.	H. Jiang et al., 2013
24.	Atherosclerosis	25 µM / L *in vitro*	D. Lu et al., 2011
25.	Cancer	20 mg/kg, 20 days, i.p.	P. Anand et al., 2008
26.	Diabetes	15 mg/kg, 6 weeks, p.o.	S.M. El-Bahr, 2013
27.	Antiviral	10 - 30 µM *in vitro*	L.S. Padilla et al., 2014
28.	Leishmanicidal	37.6 µM *in vitro*	T. Koide et al., 2002
29.	Contraceptive	300 µg/mL *in vitro*	T. Rithaporn et al., 2003
30.	Anticoagulant	25- 200 mg/kg, single dose, i.p.	R. Srivastava et al., 1985

Table 2.3: Marketed major formulations containing *Curcuma longa* extracts

S. No.	Name of formulation	Indication(s)	Manufacturer
1.	Turmeric Root Powder	Powerful antioxidant Stress management Brain support Supports healthy joints Liver function	Starland Life Enhancement Centre Site 1A, Comp 3 Craigmyle Alberta, Tojoto, Canada **www.life-enhancement.com**
2.	Organic Ground Turmeric Root	Powerful antioxidant Stress management Brain support	Frontier Natural Products Coperation 3021 78th Street, Norway Iowa- 52318, USA **www.frontiercoop.com**
3.	Turmeric supreme	Allergy Supports Heart Support Joint Support Liver Function Dietary Supplement	Gaia Herbs 101 Gaia Herbs Brevard, North Carolina 28712, USA **www.gaiaherbs.com**
4.	Turmeric capsule	Supports healthy joint function Supports normal and healthy skin	The Himalaya Drug Company Makali Bangalore Karnataka-562162, India **www.himalayahealthcare.com**

5.	Turmeric extract	Healthy Immune System Joint Support	Vita Base Limited Vitabase.com 880-C Royal Park Drive Monroe, Georgia 30656, USA **www.vitabase.com**
6.	Meriva Turmeric Complex capsule	Anti-inflammatory	Source Naturals Customer Service Department Janis Way Scotts Valley, California 9506 *,US* **www.sourcenaturals.com**
7.	Turmeric & Bromelain capsule	Enhance digestion Protect liver Healthy Joint Healthy Muscle	Natural Factors Nutritional Products Ltd. 1550 United Boulevard Coquitlam, Canada **www.naturalfactors.com**
8.	Turmeric extract capsule	Supports Healthy Joint Function Immune System	Dr .Vita Ltd Warm Spring Road Las Vegas 89113, Navada **www.drvita.com**
9.	Biomeric Turmeric extract	Skin protection	Bioprex Labs, 559/2B Plot No. 512 Marketyard Pune, Maharashtra, India **www.bioprex.com**

10.	Curcuma longa powder	Antioxidant Antimicrobial Anti diabetic	Konark Herbal And Health Care Adharu Industrial Estate Sun Mill Compound Lower Parel Mumbai-400013 Maharastra, India **www.konarkherbal.com**
11.	Turmeric extract	Antioxidant Dietary Supplement	Exim Pharm International Ashish Mahal, Golibar Santacruz (E) Mumbai - 400055, Maharashtra, India **www.exim-pharm.com**
12.	Haldi powder	Pain killer Cuts and burns Reduce cholesterol	Goodwill Herbal Product 133, MIDC, Buttibori Nagpur - 441122, Maharashtra, India **www.goodwillherbals.com**
13.	Gold Turmeric Skin Cream	Brighten skin tone Maintain skin moisture Anti-ageing	Emami limited 687 Anandapur EM Bypass Kolkata-700107, West Bangal, India **www.emamiltd.in**
14.	Vic-co Turmeric Cream	Protect Skin	Vic-co labs 78,Farmland, Ramdas peth Nagpur440010, Maharastra, India **www.viccolabs@dataone.in**

15.	Organic Turmeric	Arthritis Joint Inflammation Skin Inflammation High cholesterol Heart condition	Scortis Health Care 20-Cecil street,14-01 Equity Plaza Singapore-049705,Southern Asia **www.scortis.com.sg**

Table 2.4: Marketed major formulations containing Curcumin

S. No.	Name of formulation	Indication(s)	Manufacturer
1.	Curcumin capsule	Dietary Supplement	Genceutic Naturals 75 Commerce Drive Hauppauge New York 11788, USA **www.genceutic.com**
2.	Theracurmin capsule	Dietary Supplement Antioxidant Support Healthy joint Promote heart and vascular health	Natural Factors 14224, 167th Ave SE, Monroe Washington-A98272, USA **www.natural factors.com**
3.	Curcumin BCM -95 capsule	Enhanced Absorption	Progressive Laboratories 149 Dangay Street, Veterans Village Project 7, Quezon City, Philippines **www.progressivelabs.com**
4.	Curacel softgels	Antioxidant Improve digestive system	Euro Pharmra, Terry Naturally 955 Challenger Dr, Green Bay WI 54311, USA **www.europharmausa.com**
5.	Curcuminoid 95 plus capsule	Support Healthy joint Support liver function Support intestinal function	Vibrant Health 99 Railroad Street, Chester US **www.vibranthealth.us**

6.	R plus curcumin capsule	Enhanced Absorption Dietary Supplement Anti-inflammatory	Geronova Research 2600 Hilltop Drive Building B, Suite C120 Richmond, California 94806, USA **www.geronova .com**
7.	Curcumin C3 Complex capsule	Dietary Supplement Potent Antioxidant Cellular Health	Doctor's Best, Inc. 197 Avenida La Pata, Suite A San Clemente, California 92673,USA **www.drbvitamins.com**
8.	Livomed capsule	Hepatoprotective Immunomodulator	Oasis Pharma & Phytomolecules Ltd Village Nandpur, Lodhimajra road Nalagarh, Baddi (H.P) , India **www.oasispharma.com**
9.	Curcumin & garlic capsule	Dietary Supplement Anti Inflammatory	Wakunaga pharmaceutical Co.Ltd 4-5-36 Miyahara, Yodogawa-Ku Osaka 532-0003, Japan **www.wakunaga.co.jp**
10.	Curcumin C3 Complex & BioPerine	Antioxidant properties Protect cellular health	Doctor's Best, Inc. Suite A San Clemente, CA 92673,USA **www.drbvitamins.com**

11.	BCM (Biocurcumin) capsule	Inflammation Cancer Alzheimer's Disease Arthritis Diabetes Liver Diseases Immunomodulator Cardiovascular Disease Respiratory Disorders Gastro-intestinal Disorders Depression Antioxidant	Arjuna Naural Extracts Limited Bank Road, Alwaye Kerala- 683101, India **www.arjunanatural.com**
12.	Curcumin capsule	Inflammation Swelling Cancer care	Krishna Herbal Company 3604, Sector 23-D Chandigarh-160023, India **www.krishnaherbals.com**
13.	Herbacia capsule	Arthritis	Hindustan Herbals ltd. 51-53, IMT, Rohtak, Haryana, India **www.hindustanherbals.org**

14.	Cumax 500 capsule	Antioxidant Anti-inflammatory Antiviral	Unico pharmaceutics 5588 / 5, New Shivaji Nagar- 140008 Panjab, ludhiyana, India **www.unicopharma.com**
15.	Accumin capsule	Anticancer	Adley Formulations Sco-915, Nac Manimajra Panjab, Chandigarh, India **www.adleylab.com**
16.	Curcumin 95% USP capsule	Immune Stimulant Anti fatigue	Biomax M-2, First Floor, Paradize Tower Gokhale Rd, Naupada- 400602 Maharashtra Thane-Mumbai, India **www.biomax.co.in**
17.	Punarnva capsule	Anti-ageing	Atra Pharmaceuticals Ltd Aurangabad, Maharashtra, India **www.atrapharma.com**
18.	Curcumin C^3 complex	Antioxidant Anti-inflammatory	Sami Labs Limited 19/1, 1st Main, 2nd Phase Peenya Industrial Area Bangalore – 560058, India **www.samilabs.com**

2.2. Metformin

Metformin or dimethyl biguanide is a derivative of guanidine, and most widely prescribed drug to treat hyperglycaemia in individuals with type 2 diabetes. Guanidine is the active ingredients in *Galega officinalis*, a plant that was used in folk medicine to treat symptoms of diabetes in medieval Europe [C.J. Bailey and C. Day 1989]. Now, over 150 million people worldwide using metformin. Recently, this drug has received extra attention because many studies have suggested that diabetic patients treated with metformin exhibit a reduction in cancer incidence [J.M. Evans et al., 2005; G.G. Libby et al., 2009; G.W. Landman et al., 2010]. Some other reports also revealed its therapeutic potential in other conditions, including diabetic nephropathy, neuroprotection, cardiovascular diseases and polycystic ovary [M. El-Mir et al., 2008; A.M. Sharma and A.Golay 2002]. It is accepted that the main effect of this drug is to decrease hepatic glucose production through a mild inhibition of the mitochondrial respiratory chain complex I [R.S. Hundal et al., 2002; M. Takashima et al., 2010]. It has also been proposed that metformin suppresses hepatic glucose production through the activation of AMPK pathway, which further inhibits the hepatic glucogenic and lipogenic gene expression [X.Y. Zhou et al., 2004; R.J. Shaw et al., 2005]. Metformin is not completely absorbed from the gut. Its bioavailability is only 40–60 %. There are three different families of transporters involved in the transport of metformin viz. organic cation transporters (OCTs) [J. Muller et al., 2005], multidrug and toxin extrusion transporters (MATEs) [F. Staud et al., 2007] and plasma membrane monoamine transporter (PMAT) [M. Zhou et al., 2007]. More recently, serotonin transporter and choline high-affinity transporter have also been described as being involved in the absorption of metformin [T.K. Han et al., 2015]. Drug that inhibit or induce the transporters have the potential to interfere with the

transport of metformin and ultimately affect both plasma and intracellular concentrations of metformin. Previous studies demonstrated that metformin can rapidly cross the blood brain barrier (BBB) and has several beneficial effects in the brain such as anti-inflammatory and neuroprotective effects [K. Labuzek et al., 2010; F. Takata et al., 2013].

2.2.1. Pharmacological activities

Metformin is pleiotropic molecule which attributed to its various pharmacological activies.

2.2.1.1. Metformin and cardiovascular disease: There is evidence that metformin can offer protection against cardiovascular disease (CVD) in diabetic patients. The results of multiple studies suggest that metformin can protect against atherosclerosis by promoting endothelial integrity and preventing the formation of plaques. Activation of AMPK by metformin limits endothelial cell damage caused by oxidative stress elevated under hyperglycaemic conditions [B. Batchuluun et al., 2014]. The resulting reduction in cytosolic reactive oxygen species (ROS) generation halts the initiation of mitochondrial ROS, which in turn prevents the triggering of endothelial apoptosis [M.P. Bhatt et al., 2013].

2.2.1.2. Metformin and cancer: Metformin garnered considerable interest within the field of oncology during 2005. Numerous observational studies have supported a protective role for metformin against a variety of cancer types including liver, pancreas, colorectal, oesophagus and stomach cancer in diabetics [M. Franciosi et al., 2013]. Both experimental and epidemiological evidence suggests that insulin and insulin-like growth factor 1 (IGF-1) can promote tumorigenesis by stimulating the proliferation of epithelial cells [M. Pollak, 2008]. Metformin may prevent such neoplastic activity by reducing hyperinsulinaemia and lowering levels of these signalling molecules. Metformin can also modify inflammatory processes known to play a keen role in cancer progression. It has also been reported that metformin

blocks the activity of the transcription nuclear factor-κB (NF-κB) resulting in decreased secretion of pro-inflammatory cytokines by senescent cells [O. Moiseeva et al., 2013].

2.2.1.3. Metformin and the gut microbiota: Some interesting reports provide a link between alterations to the microbiota in the gastrointestinal tract (caused by changes in diet and environmental conditions such as antibiotics) and nutrition-related syndromes such as obesity, type 2 diabetes, metabolic syndrome, cancer and aging [I. Cho and M.J. Blaser 2012; M.J. Claesson et al., 2012], suggesting that the gut microbiota could act as a potential biomarker for host health. Metformin led to increase in goblet cells, producers of mucin, a nutrient source for the mucin-degrading bacteria *Akkermansia municiphila*. In fact, probiotic administration of this bacterial strain or metformin is associated with an improved metabolic profile, reducing metabolic endotoxemia, adipose tissue inflammation and improved glycaemic control and insulin resistance [N.R. Shin et al., 2014; A. Everard et al., 2013]. Lactobacillus is one of the many bacteria that can utilize glucose to produce lactate. Notably, effects of metformin in improving glucose homoeostasis in high-fat mice are abolished through a cocktail of broad-spectrum antibiotics [N.R. Shin et al., 2014]. These data suggest that gut microbiota is a target of metformin to produce its effects on host physiology.

2.2.1.4. Metformin and CNS: Metformin has also been shown to increase neurogenesis, spatial memory formation and reduce the risk of Parkinson's disease, protect against haloperidol-induced catalepsy via inhibition of oxidative/nitrosative stress and lipid peroxidation [A. Halimah et al., 2014]. Metformin has been shown as a neuroprotectant against apoptotic cell death in primary cortical neurons [M.Y. El-Mir et al., 2008]. It has also been reported to protect the brain against the oxidative imbalance promoted by diabetes mellitus [S. Correia et al., 2008]. Increased neuronal viability has been reported by

metformin treatment in an *in vitro* model of ischemia [J.G. Mielke et al., 2006]. It has also been reported that widely known role of metformin as a neuroprotectant, is responsible to protect against neurodegenerative diseases, like Alzheimer's [A. Gupta et al., 2011] and huntington's disease [T.C. Ma et al., 2007].

2.3. Diabetes Mellitus

Diabetes mellitus is a group of syndromes characterized by hyperglycemia, altered metabolism of carbohydrates, lipids and proteins, which ultimately leads to cause macro vascular and microvascular complications [S. N. Davis, 2006; E.A.M. Khalil et al., 2004]. Diabetes mellitus is a slowly progressing chronic metabolic disorder where pancreas was unable to produce adequate insulin or the body develops resistance to insulin it produces [N. Tiwari et al., 2014; S. Kahn, 2001]. World Health Organization (WHO) and Current International Diabetes Federation report says that, diabetes mellitus is possibly the world's fastest growing metabolic disorder, and the global prevalence of diabetes is expected to rise from 422 million people in 2015 to approximately 590 million by 2035. WHO projects that diabetes will be the 7th leading cause of death in 2030. Many studies from different parts of the world have revealed that, occurrence of diabetes was high in urban population and it is classified under life style disorders [M. Ragunathan and N. Ragunathan, 1992]. Chronic hyperglycemia is a characteristic of the diabetic condition, while glucose toxicity is the main cause of diabetic complications, which are often observed only several years after the beginning of the illness [J.E. Reusch, 2003]. Hyperglycemia itself reduces the insulin secretion capacity of pancreatic β-cells, and the resultant increase in insulin resistance leads to further hyperglycemia. This vicious circle finally leads to the total incapacity of β-cells to secrete insulin properly [D. LeRoith, 2002; M. Dubois et al., 2007]. Glucose homeostasis is

primarily controlled by the anabolic hormone insulin and also by some insulin-like growth factors [D.B. Dunger, 1995]. Several catabolic hormones (glucagons, cortisol, catecholamines, growth hormone and adrenocorticotropic hormone) may antagonize the action of insulin and are known as anti-insulin or counter regulatory hormones [J.E. Gerich and P.J. Campbell 1988]. It has been found that oxidative stress is associated with the molecular mechanism of the decreased insulin biosynthesis and secretion, which is the main etiology of glucose toxicity. Metabolic reactions continuously produce reactive oxygen species (ROS), such as superoxides (O_2^-), hydroxyl radicals (OH^-), peroxyl radicals (ROO^-) or nitric oxide. ROS are involved in a diversity of biological phenomena, such as inflammation, carcinogenesis, aging and atherosclerosis. However, several antioxidant enzymes help to maintain low levels of reactive oxygen species. Oxidative stress corresponds to the overproduction of ROS that can damage cellular components, such as lipids, proteins or DNA [A.M. Vincent et al., 2004]. There are strong indications that oxidative stress may be a key event in diabetic complications [J.W. Baynes and S.R. Thorpe, 1999; Y. Brunner et al., 2009]. Hyperglycemia-induced oxidative stress is also involved in the development of both macrovascular and microvascular diabetic complications [G.L. King and M.R. Loeken 2004]. Therefore it has been suggested that glucose homeostasis is essential to inhibit diabetes induced and associated co morbidities.

2.4. Co-morbid Brain Disorders Associated with Type-2 Diabetes

Type-2 diabetes has been associated with various comorbidities including CNS disorders such as depression, anxiety, pain and inflammation. Neuronal glucose uptake depends on the extracellular concentration of glucose, and cellular damage can ensue after persistent episodes of hyperglycemia. Hyperglycaemia in diabetes causes up to fourfold increases in

neuronal glucose levels. Its persistent episodes increases intracellular glucose metabolism which leads to neuronal damage; this phenomenon is often referred to as glucose neurotoxicity. Glucose toxicity causes oxidative stress is critical, in term of cellular function disturbance and by generation of more reactive molecules from glucose [T. Nishikawa et al., 2000]. These molecules then combine with cellular and extracellular macromolecules, altering their functional properties and causing downstream adverse effects on cell function. Such changes in cellular function give rise to diminished neurotrophic support, disturbed excitability and impulse conduction and the generation of painful states [A.J.M. Boulton et al., 1982]. In the longer term, Schwann-cell death and axonal degeneration lead to complete functional breakdown [I.G. Obrosova et al., 2005]. This condition further leads to other co-morbid brain disorders.

2.4.1. Diabetes and depression

Depression as per the World Health Organization (WHO) represents a common mental disorder. It is characterized by depressed mood, loss of interest or pleasure, feelings of guilt or low self-esteem, disturbed sleep or appetite and poor concentration. Diabetes and depression are two major chronic diseases with bidirectional relationship and both of them are spreading like epidemics in almost all countries around the world [E.H. Lin et al., 2010]. Co-occurrence of these two pathologies in same patients has strong negative impacts on their quality of life and shortens their life span [J. Dirmaier et al., 2010; T. Roy et al., 2012]. It has been reported that prevalence of depression in diabetic patients is higher than prevalence of depression in normal population [R.J. Anderson et al., 2001]. Numerous structural, behavioural and biochemical alterations of the central nervous system are observed in diabetic patients and diverse such alterations are also observed in rodent models of diabetes

where exaggerated symptoms of depression, anxiety was observed [L.A. Hilakivi-Clarke et al., 1990; G.M. Husain et al., 2011a; N.E. Rowland and L.L. Bellush 1989]. All the three major neurotransmitters viz. serotonin, adrenaline and noradrenaline have been identified to be involved in pathophysiology of depression. The currently available medication for treating depression, mainly restore the imbalance of monoaminergic transmission either by inhibiting the metabolism of monoamines or by inhibiting their reuptake at synapse [M.J. Owens et al., 1997]. The neuronal adaptative mechanisms of these receptors, both presynaptic and postsynaptic, account for the delay and limited response to the antidepressant drug [P. Celada et al., 2004].

The antidepressant drugs may be classified into reversible inhibitors of monoamine oxidase, tricyclic antidepressant, selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitor, and atypical antidepressants [M.S. Stahl, 2009]. Treatment of depression by modern medicine has several shortcomings. Most medications for major depression have strong side effects [M.S. Hamilton and L.A. Opler, 1992; J. A. Johnston et al., 1991; A.H. Glassman et al., 1993]. Chances of reoccurrence are also high with treatment of depression by modern medicine [A.C. Viguera et al., 1998]. Thus, search for effective and safer medications for comorbid depression is necessary and plant derived products can prove to be a better option for that.

2.4.2. Diabetes and anxiety

Anxiety has also been associated with poor glycemic control seen in diabetes. According to a survey based study it was found that compared to rates seen in the general population, the rates of anxiety disorder are higher (40 % of diabetic patients have elevated levels of anxiety symptoms) in diabetic patients [A.B. Grigsby et al., 2002]. In addition, recent clinical studies

have shown the prevalence of anxiety in diabetic patients is much higher than the normal population, supporting the notion that there is strong relationship between diabetes and anxiety disorder [M. Clavijo et al., 2006]. Anxiety in patients with diabetes is associated with less frequent blood glucose monitoring and suboptimal glycemic control [M.C. Shaban et al., 2006], which further worse the diabetic condition.

Benzodiazepines (BZDs) have been used as the drug of choice for the treatment of anxiety disorders. However, long-term uses of BZDs do have various side effects such as development of tolerance, emergence of withdrawal symptoms and cognitive impairment [L.A. Papp et al., 2010]. The currently available clinical treatment of anxiety includes use of BZD, sedatives, antihistaminic and β blocker. However, the side effects associated with these treatment modalities have motivate to search for alternate treatment system with lesser side effects [L.A. Papp et al., 2010].

2.5. Inflammation and Pain Associated with Type-2 Diabetes

Diabetes mellitus has become the most common cause of peripheral neuropathy and many diabetes patients suffer from chronic pain. Central sensitization plays a pivotal role in the pathogenesis of pain hypersensitivity [C.A. von Hehn et al., 2012] and its development results from augmented spontaneous burst discharges of primary sensory neurons in neuropathic pain [R. Amir et al., 2002]. Similar to traumatic neuropathic pain, microglia activation is involved in the development and maintenance of central sensitization in diabetic neuropathic pain. Since activity in primary afferents is decreased in diabetes, the development of hypersensitivity of spinal nociceptive neurons in diabetic neuropathic pain must involve in some mechanisms that are distinct from traumatic neuropathic pain.

Glucose toxicity on local site of spinal cord can contribute to the development of spinally mediated hyperalgesia and targeting on spinal sensory processing may assist development of novel therapeutic strategies for preventing and alleviating painful diabetic neuropathy [N.A. Calcutt 2002; N.A. Calcutt, 1997]. Hyperglycemia is an important factor in pain hypersensitivity associated with diabetes and results in altered pain sensitivity. Appropriate blood glucose control can help relieve pain in long-term diabetes through indirect mechanisms [C. Courteix et al., 1993]. The high concentration of glucose results in pain hypersensitivity characterized by allodynia and hyperalgesia [K. Pabreja et al., 2011] probably by disrupting the functions of cell mitochondria and subsequent generation of reactive oxygen species [M.J. Stevens et al., 2000] and oxidative stress [E.L. Feldman 2003].