CHAPTER-1

INTRODUCTION

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Curcuma longa L., belongs to the family Zingiberaceae, is a perennial herb and also known as turmeric. It is often referred as "*Indian Solid Gold*" and "*Indian Saffron*" due to its yellow colour. In Ayurveda, turmeric has been used internally as a stomachic, tonic and blood purifier and externally in the prevention and treatment of several skin diseases. Traditional Indian medicine claims the use of its powder against biliary disorders, coryza, cough, wounds, hepatic disorder, rheumatism and sinusitis [H.P.T. Ammon et al., 1992]. Currently it is phytochemically and pharmacologically one of the more extensively studied, edible plant derived products of medicinal uses. Numerous reviews and research reports describing diverse therapeutic possibilities of the plant and its bioactive secondary metabolites have appeared during recent years [S.A. Chaudhary et al., 2010; S.C. Gupta et al., 2013; B. Chempakam and V.A. Parthasarathy 2008]. Amongst numerous other identified bioactive and therapeutically interesting secondary metabolites of turmeric, mainly three structurally and functionally analogous diarylheptanoids viz. curcumin, desmethoxycurcumin, and bis-desmethoxycurcumin (collectively referred to as curcuminoids) have attracted the most attention of modern herbal researchers and drug discoverers [B.B. Aggarwal et al., 2007; B. Ahmed 2014; L. Alappat and A.B. Awad 2010; P.G. Bradford, 2013; G. Grynkiewicz and P. Slifirski 2012; G.K. Jayaprakasha et al., 2006]. The numbers of reports reconfirming broad spectrum of microbicidal efficacies of curcumin and other turmeric curcuminoids have continued to increase during more recent decades [S.Z. Moghadamtousi et al., 2014; S. Prasad et al., 2014]. They have added experimental evidences in support of their medicinal and dietary uses in diverse traditionally known systems of medicine and health care. It is also suggested that they are structurally and functionally unique drug leads, and they could be potentially useful for prevention and cure of diverse spectrums of psychopathologies and

metabolic disorders. Available preclinical and clinical information on turmeric curcuminoids not only reveal that they are pleiotropic protective agents, but also suggest that improving their oral bioavailability could be feasible means for obtaining therapeutic benefits from them [S. Davinelli et al., 2012; S.C. Gupta et al., 2013; P Anand et al., 2007; P.S Patel et al., 2014]. Despite of such advances though, many questions concerning their pharmacological sites and modes of actions are still remaining controversial and speculative only [A. Goel et al., 2008; T. Esatbeyoglu et al., 2012]. Analogous is also the situation for numerous other edible and other phytochemical isolated from traditionally known medicinal and edible plants commonly used in diverse traditionally known systems of medicine, or in modern nutritional therapies. It has also been suggested that numerous edible phytochemicals contribute to their physical and mental health benefits might be due to modulation or regulation of brain plasticity [C. Rooney et al., 2013; T. Murphy et al., 2014]. Therefore, we have identified, standardized and pharmacologically validated a mouse bioassay system for detecting metabolic as well as brain function modulating potentials of medicinal plant extracts and their known bioactive constituents [A.K. Thakur et al., 2014; A.K. Thakur et al., 2015; A.J. Langstieh et al., 2014]. During the course of such efforts it was observed that repeated daily treatments with the antidiabetic drug metformin effectively suppresses diverse physiological stress responses in mice, and its observed effects are quite analogous to those of several edible phytochemicals [A.J. Langstieh, et al., 2014]. Vast majorities of therapeutically interesting bioactivities of metformin known to date [C. Pulito et al., 2013] are quite analogous to those of curcuminoids. It has also been reported that in cellular and other *in vitro* models the curcuminoids are several hundred fold more effective than the antidiabetic drug [T. Kim et al., 2009]. Therefore, it was of interest to experimentally verify the possibility that metformin like stress response modulating efficacies of curcuminoids are also involved in its therapeutically interesting bioactivities observed in animal models. Many questions

concerning oral bioavailability, doses and treatment regimen necessary for obtaining therapeutic benefits from curcuminoids and known other bioactive secondary metabolites of turmeric, yet cannot be answered with any certainty [P. Anand et al., 2007]. Some observations made *in vitro*, suggested that oral bioavailability of curcuminoids from turmeric could as well be higher than those of pure curcuminoids [M. Maheshwari, 2010]. These observations clearly suggest that health benefits of curcuminoids and other turmeric phytochemicals are either due to their bioactive metabolites, or due to its non-systemic effects. Since turmeric is always consumed with other food ingredients containing diverse other bioactive molecules with broad spectrums of bioactivity profiles, it is almost certain that traditionally known health benefits of turmeric, cannot entirely be due to its curcuminoids contents, or on their blood levels observed after its intake. Numerous preclinical and clinical studies indicated the great potential of curcumin in treating several diseases, but the application of curcumin in the therapeutic treatment was hindered by its poor systemic bioavailability. In any case, available information on bioavailability of curcumin and several other bioactive constituents of *Curcuma longa* extracts clearly reveal that more than 90% of their orally administered doses are extensively bio-transformed within the gastrointestinal tract [Y.J. Wang et al., 1997], and can alter diverse drug metabolizing activities in liver and other peripheral organs [G. Srivastava and J. Mehta 2009]. Therefore, it can be expected that the long lasting therapeutically interesting bioactivities of curcumin and its other curcuminoids, observed in experimental animals after its oral administrations might be due to its irreversible interactions with biologically important macromolecules within the gastrointestinal tract. Therefore several efforts have been made during this study to better understand the Ayurvedic pharmacology of *Curcuma longa* extract in terms of modern medicinal system.

Several studies have demonstrated that curcumin, which is polyphenol fraction of *Curcuma longa* function as an antioxidant, anti-inflammatory and anti-atherosclerotic, inhibits scarring, cataract and gallstone formation. It also promotes wound healing and muscle regeneration, prevents liver injury and kidney toxicity, and exerts medicinal benefits against psoriasis, diabetes, multiple sclerosis, septic shock, Alzheimer's, HIV disease, lung fibrosis, cardiovascular disease, arthritis and inflammatory bowel disease [B. Aggarwal et al., 2003; R. Sharma et al., 2005; B. Aggarwal and S. Shishodia 2006; X.Y. Qin et al., 2010]. Recently, much attention has been paid on the neuroprotective and neurotherapeutic potential of curcumin and its other curcuminoids [S.K. Kulkarni and A. Dhir 2010]. Because of the increasing evidence that the pathogenesis of type 2 diabetes mellitus is connected to inflammation, curcumin has arises as a potential drug of interest for diabetic pharmacology [B. Aggarwal 2010; A. Shehzad et al., 2011]. Recent preclinical observations made in our laboratories and elsewhere strongly suggest that curcuminoids could be promising therapeutic lead for prevention and treatment of co-morbidities commonly associated with diabetes and diverse other chronic diseases [S. Verma et al., 2015; S. Verma et al., 2016a; S. Verma et al., 2016b].

Comorbidities of depression and anxiety are often encountered in patients suffering from, or prone to diabetes and other chronic health diseases [A. Bystritsky et al., 2014]. These are mostly accompanying medical conditions for which traditionally known medicinal uses of *Curcuma longa* extracts are known since centuries. Recent observations, revealing that curcumin and diverse other turmeric constituents modulate the functions of stress responses mediated by shock proteins [R.E. Ali and S.I. Rattan 2006; A. Speciale et al., 2011]. Therefore, experimental evidences reconfirmed the convictions that stress response regulating effects of turmeric derived products are involved in their modes of action. However, the possibility that *Curcuma longa* extracts possess anti-stress or adaptogenic properties have

often been pointed out by several modern scholars and researchers of traditionally known herbal remedies [N. Bhatia et al., 2011]. Therapeutically interesting preclinical information on medicinal phytochemistry and pharmacology of *Curcuma longa* extracts and curcuminoids strongly suggest that they are promising therapeutic leads potentially useful for treatments of diverse spectrums of psychopathologies commonly encountered in almost all lifestyle associated chronic diseases [M. Nabiuni et al., 2011]. Since their high efficacy and broad safety profiles have already been demonstrated in appropriately controlled and properly designed clinical trials necessary for firmly establishing their psychotherapeutic potentials. Such efforts should eventually, not only be useful for identifying validated novel pharmacological targets urgently needed for discovery and development of drugs against neurological disorders associated with metabolic disorders, but also for better understanding of biological principles and processes involved in traditionally known widespread medicinal and health care uses of *Curcuma longa*.

Metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease, obesity and diabetes. Metabolic syndrome is generally associated with diabetes mellitus, obesity, blood lipid disorders, inflammation and insulin resistance [J.P. Despres and I. Lemieux 2006]. The International Diabetes Federation has estimated that the worldwide prevalence of diabetes mellitus is expected to increase from 422 million people in 2015 to 592 million by 2035. Diabetes has been associated with various disorders including brain disorders such as depression and anxiety. Several co-morbid conditions have been described in rodent models of diabetes including depression and anxiety [N.E Rowland and L.L. Bellush 1989]. Despite of extensive efforts and considerable progress, proper pharmaco-therapeutic management of comorbid mental health conditions often associated with almost all chronic health problems still remain to be one of the major challenges for medicine [J.B Detweiler-Bedell et al., 2008]. It is now well established, that

diverse types of chronic mental as well as physical stress are the root causes of such disorders, and that adaptation to stress-induced syndromes could be a feasible means for combating them.

Available therapy for neurological disorders is often associated with several undesirable side effects. Unfortunately, currently available psychoactive drugs do not meet the therapeutic demands of diabetic patients and many of them are even contraindicated for patients with diabetes. Therefore aim of the study was to evaluate orally efficacious and standardized extract of *Curcuma longa* to compare its pharmacological profiles with metformin to explore its potential role in the management of comorbid neurological disorders generally associated with diabetes followed by elucidation of their mechanism(s) of action(s). Observed analogous activity profile of 95.49% enriched *Curcuma longa* extract with metformin strongly suggest its significant adaptogenic activity and promising therapeutic role for prevention and cure of diverse mental health problems and other comorbidities commonly associated with, or caused by diabetes.

The present study was designed to cover the following objectives:

- Comparative pharmacological evaluation of four different extracts of *Curcuma longa* for selecting most effective one.
- Pilot study cum dose finding study of *Curcuma longa* extract (CLE) containing 95.49% curcuminoids.
- To compare the different pharmacological activities of *Curcuma longa* extract with metformin.
- To explore the potential of *Curcuma longa* extract in the management of diabetes and its associated anxiety and depression like disorders followed by elucidation of their mechanism of action.