Anti-obesity mechanism of *Curcuma longa* L. - An over view

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Chronic low grade inflammation is one important reason for the development of obesity and the inflammation is initiated by excess nutrient from metabolic cell and is characterized by increasing TNF$\alpha$, interlukins, cytokinines, etc. Besides this, genetic, social, behavioural and environmental factors alone or interaction with each other influences diet, physical activity by affecting complex hypothalamic neuro-circuitry. These increase leptin level, inflammatory mediators and reactive oxygen species (ROS), which positively correlate with obesity. *Curcuma longa* L., commonly known as *Haridra* have been used for treatment of obesity and diabetes since ancient time in Ayurveda, the Indian traditional system of medicine. From current research, it has been observed that *C. longa* inhibit secretion of leptin, pro-inflammatory mediators and over production of ROS, whereas it increases secretion of insulin, adiponectin in plasma. Increased serum adiponectin insulin and decreased production of ROS negatively correlate with obesity. In addition to these, *C. longa* inhibit early growth response (Egr-1) gene, which is related to development of obesity. It is clear that by affecting leptin, adiponectin, inflammatory mediators, ROS, regulating nutritional environment and Egr-1 gene, lipogenic gene and ob gene, *C. longa* may be affirmative for management of obesity.

**Keywords**: *Curcuma longa* L., Inflammatory mediators, Obesity, Reactive oxygen species.

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**Introduction**

Chronic inflammation has been recognized as important aspect in pathogenesis of obesity$^1$ and the inflammatory response in the obese state is quite different than the normal inflammation$^2$. This may be best described as metaflammation$^3$, i.e. a chronic, low-grade inflammatory response initiated by excess nutrients in metabolic cells. The metabolic signals emerging from metabolic cells initiate the inflammatory responses and impair metabolic homeostasis. It is revealed by increased level of TNF-$\alpha$$^4$, interleukin (IL)-6, IL-1$\beta$, CCL2 and others$^5$ in adipose tissue. Liver$^7$, pancreas$^8$ and skeletal muscle$^9$ are the primary site of cytokine expression indicating hallmark of the metabolic inflammation in obesity. Obesity is a complex trait influenced by genes, diet and physical activity$^{10}$. It was reported that genes, peptides, neurotransmitters and receptors in hypothalamus and neighboring area regulate appetite and body weight$^{11}$. Regulation of appetite is a complex hypothalamic neuro-circuitry in which arcuate nucleus and hormones namely leptin and ghrelin play an important role$^{12}$ along with other factors like social, behavioural and environmental factors, alone or in interaction with each other. The molecular mechanism of pathogenesis and these factors will enlighten the treatment strategies of weight reduction.

Natural plant products have been used throughout history for various purposes; to investigate the effects of natural origin compounds on human health either for prevention or treatment of diseases$^{13}$. *Curcuma longa* L. belonging to Zingiberaceae family and commonly known as Turmeric is extensively used as a spice, food preservative and colouring material$^{14}$ in South East Asia. It has been traditionally used in remedy for various diseases, including anorexia, diabetes, obesity$^{15}$, hepatic disorders, etc. Table 1 gives some classical and proprietary formulation for obesity having *Haridra*. In last few decades, extensive work has been done to establish the biological and pharmacological activity of turmeric and it has been reported that Curcumin (diferuloylmethane), the main yellow bioactive component of turmeric has a wide spectrum of pharmacological actions such as anti-inflammatory, antioxidant, anti-diabetic, anti-bacterial, etc.$^{16}$. Due to the presence of these
pharmacological properties \textit{C. longa} shows beneficial effect in management of obesity, diabetes, etc. and in the present review, possible mechanism by which \textit{C. longa} is supportive in management of obesity has been discussed.

**Mechanism of \textit{C. longa} towards management of obesity**

Obesity arises from the imbalance between caloric intakes and energy expenditure and it occurs as a consequence of our modern lifestyle\cite{17}. In addition, familial factors such as family structure, lifestyle, nutritional environment, meal patterns and family stressors are equally important in the development and maintenance of obesity\cite{18}. \textit{Haridra} having wide spectrum of activity like anti-oxidant, anti-inflammatory, influence on nutritional environment as well as genetic point may be beneficial for the management of obesity.

**Effect of \textit{C. longa} on nutritional environment**

Nutritional environment is the place where people buy or eat food and it contributes to the increasing epidemic of obesity. The obesity may be caused by abnormal carbohydrate and fat metabolism, so an attempt has been made to review the effect of \textit{C. longa} on their metabolism.

**Effect on carbohydrate metabolism**

Weight gain is associated with carbohydrate intake\cite{19,20}. Insulin decreases blood glucose levels by suppressing hepatic glucose production, increasing glucose uptake into muscle and increasing adipose

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<tr>
<td>Karshan and Lekhaniya Gana</td>
<td>\textit{Haridra} (\textit{Curcuma longa}), Dara haridra (\textit{Berberis aristata}), Chitrak (\textit{Plumbago zeylanica}), Vacha (\textit{Acorus calamus})</td>
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tissue expression of GLUT4. It is reported that, down regulation and over-expression of GLUT4 (a major contributing factor for impaired insulin-stimulated glucose transport in obesity) enhances insulin sensitivity and glucose tolerance. It has been reported that curcumin increases glucose uptake by skeletal muscle mediated by improving the expressions of GLUT4 through the PLC-PK3 pathway. Thus C. longa increases calories consumption by enhancing glucose utilization by muscles which helps in management of obesity.

**Effect on Lipid metabolism**

Increased fat mass present in obesity is an imperative risk factor for diabetes and cardiovascular disease. The alteration in lipid metabolism may arise due to imbalance between fatty acid synthesis, uptake and β-oxidation, i.e. imbalance between adipogenesis and lipolysis. Adipogenesis is a differentiation process by which undifferentiated pre-adipocytes are converted to mature adipocytes. During this, SREBP-1c stimulates the expression of C/EBPα, PPAR-γ and lipogenic enzyme such as fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) that induces the conversion of acetyl-CoA into fatty acids and triglycerides. Lipolysis is the key process of triglyceride breakdown, which is ultimately converted into energy through β-oxidation that may be helpful for achieving weight loss and enzyme such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) are responsible for lipolysis. ATGL initiates lipolysis by specifically removing free fatty acids to produce a diacylglycerol, which is further hydrolysed by HSL. It is reported that ethanolic extract of C. longa decreases the expressions of FAS, ACC, peroxisome proliferators-activator receptor-γ (PPAR-γ) and enhancer binding protein-α (C/EBPα). In this way, it inhibits the synthesis of cholesterol/triglycerides. Furthermore, C. longa up-regulate the expression of lipases such as ATGL, HSL, adiponectin and AMP-activated protein kinase (AMPK) phosphorylation which causes lipolysis. Thus, C. longa is beneficial for treatment of obesity by inhibiting adipogenesis as well as activating lipolysis.

**Effect of C. longa on Endocrine system**

Obesity arises due to imbalance between energy intake and energy expenditure (basal metabolic rate and biochemical processes). The excess energy is chiefly stored in adipose tissue in the form of triglycerides and act as endocrine organ for the regulation of lipid homeostasis. It has been reported that adipocyte (adipose cell) secrete different type of proteins (adipokines) such as leptin, adiponectin, interleukin-6 (IL-6) and plasminogen activator inhibitor-1 (PAI-1), which are directly or indirectly involved in regulation of lipolysis. Among them, serum level of leptin is regulator of food intake, energy expenditure and is positively correlated with BMI. Serum level of adiponectin is negatively correlated with BMI, waist to hip ratio as well as obesity. Curcumin (active principle present in C. longa) blocks the leptin signaling by reducing the phosphorylation levels of the leptin receptor (Ob-R) and increases the induction of adiponectin, which improves obesity. It also improves insulin sensitivity and elevate serum insulin level, which strongly enhances adiponectin expression (two fold) and secretion (three fold). In this way serum insulin up regulates adiponectin expression. Curcumin induced electrical activity in β-cells of pancreas by activating volume-regulated anion (channel f) with depolarization of the cell membrane which enhances insulin release. Thus, by reducing serum leptin concentration, enhancing adiponectin and serum insulin, C. longa is helpful in reducing body weight.

**Anti-inflammatory activity of C. longa**

Subclinical or chronic inflammation has been recognized as major component in development of obesity by initiating inflammatory response. Due to this initiation adipose tissue secrete adipokines like tumour necrosis factor-α (TNF-α), IL-6, etc. TNF-α increases systemic insulin resistance by promoting release of fatty acid from adipose tissue in to blood vessels and IL-6 increases lipolysis, fat oxidation in human causing further insulin resistance. Curcumin down regulate expression of various pro-inflammatory cytokines including TNF-α, interleukins by inactivation of the nuclear factor-kappa B (NF-kB) i.e. it suppresses secretion of TNF-α and IL-6 by inhibition of NF-kB and up regulate adiponectin secretion. Adiponectin acts as anti-inflammatory and insulin-sensitizing hormone and also inhibits production of TNF-α. It has also been reported that obesity is the result of excessive adipogenesis and inhibition of differentiation of 3T3-L1 cells to adipocytes may be beneficial for the prevention of obesity. C. longa inhibit adipocyte differentiation in dose dependent manner and also alter the expression of genes involved in the adipogenesis. Thus, by increasing concentration of...
adipokine, inhibiting pro-inflammatory mediator and inhibiting adipocyte differentiation, *C. longa* may help in reducing body weight.

**Anti-hypoxic activity of *C. longa***

Hypoxia (low O$_2$ availability) may change the expression of pro-inflammatory mediators and inhibit enzymes such as lipoprotein lipase related to lipid metabolism. It induces expression of hypoxia induced factor (HIF-1α), pro-inflammatory mediators, lactate concentration, glycerol release, reactive oxygen species (ROS) production, reduces antioxidant enzymes (superoxide dismutase and catalase) status and insulin resistance. All these factors favour the pathogenesis of obesity.

*C. longa* has been used for centuries in Ayurvedic and traditional Chinese medicine for its anti-inflammatory properties. Curcumin, the major component of *C. longa* reduces HIF-1α protein concentration by 70%. Furthermore, others extract of *C. longa* such as de-methoxy-curcumin and bis-demethoxy-curcumin have free radical-scavenging activities whereas the polyphenol component improves insulin sensitivity. Thus, it can be said that *C. longa* reverses the pathogenesis of obesity mediated by hypoxia.

**Anti-oxidant activity of *C. longa***

Oxidative stress is imbalance between generation of free oxygen radicals and antioxidant defence system, estimating the reducing power/antioxidant capacity. The increased ROS seems to be involved in the control of body weight, by exerting effects on hypothalamic neurons that control satiety and hunger behaviour. Obesity is associated with increased oxidative stress at the level of adipocyte mitochondria because processing of excess fatty acids causes mitochondrial uncoupling, increasing the release of ROS. When caloric intake exceeds energy expenditure, the substrate-induced increase in Kreb’s cycle activity generates an excess of ROS. Thus, excessive intake of macronutrients induces ROS generation and excess ROS generation favour oxidative stress, which is responsible for development of obesity. Curcumin have antioxidant property, i.e. it decreases ROS load to divert ROS to other reaction pathways that form less reactive products, inhibit free radical production and prevent the protein glycosylation and lipid peroxidation. Antioxidants also act as a replicable or recyclable “buffer” to absorb oxidative hits and excess energy. Furthermore, curcumin also enhances the activity of many antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase (GPx), and heme oxygenase-1 (OH-1), which reduces the oxidant status present in body. Thus, by decreasing ROS load and increasing the antioxidant enzyme, *C. longa* breaks down the pathogenesis of obesity caused by oxidative distress and is helpful in reduction of body weight.

**C. longa enhances energy business***

FAS, a key enzyme participating in energy reservation, is related to various human diseases like obesity. FAS inhibitors reduce food intake and body weight. Curcumin, down-regulate hepatic FAS and up-regulate fatty acid β-oxidation activity, i.e. inhibit FAS and increased β-oxidation. Increase β-oxidation decreases fat storage, increases insulin sensitivity and produces hypolipidemia that play an important role in the prevention of hyperlipidemia.

AMPK is cellular energy and stress sensor that promotes the activation of energy restorative (catabolic) processes and inhibition of energy consumptive (anabolic) processes, which inhibits FAS, stimulates carnitine palmitoyltransferase-1 (CPT-1) and β-oxidation of fatty acids, i.e. it helps in reduction of body weight. Curcumin activated AMPK causes increased catabolic process, i.e. increased consumption of energy, which is related to the reduction of body weight.

**Effect of *C. longa* on genetic factors***

Obesity appears to be the result of interaction of paramount genetic factors with an abundance of calorie dense food and decline in physical activity. It has been estimated that heritability of body mass index is between 40–70% in children and adults and other anthropometric measures of obesity and regional fat distribution (Skin fold thickness, waist circumference and waist : hip ratio) show similar heritability. The early growth response (Egr-1) gene, transcription factor modulates the activity of PAI-1 that has been associated with insulin resistance and obesity. Curcumin inhibits the expression of the PAI-1 by reducing the activity of Egr-1, it also inhibits the differentiation of pre-adipocytes to adipocytes and inhibit adipokine-induced angiogenesis of human endothelial cell through suppression of VEGF-a.

It has been reported that transcription factors such as ChREBP and SREBP-1c stimulate lipogenic gene expression and augmented lipogenic gene expression may also contribute to the development of
Obesity. It is reported that Curcumin represses SREBP-1c and ChREBP expression with repression of L-PK, which down-regulate the activity of lipogenic gene expression and by doing this curcumin prevents obesity and its associated metabolic defects. Furthermore, the overexpression of ob-gene may increase the adipocytokine, which ultimately causes obesity through anti-inflammatory, oxidative stress and dysregulation of leptin, insulin and adiponectin. Curcumin also suppresses the Ob-R gene expression. Thus C. longa may be beneficial for reduction of obesity by modulating the activity of Egr-I gene, lipogenic gene and ob gene.

Conclusion

Obesity is a complex disorder caused by chronic inflammation, oxidative stress as well as abnormal behaviours; biological pathways may also contribute to the development of obesity. C. longa is effective against inflammation, oxidative stress, increases adiponectin concentration, maintains harmony of nutritional substances, influences genetic point and hence may be beneficial for the management of obesity.

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