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

Kapil Deo Yadav* and Anand K Chaudhury

Department of Rasa Shastra, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, Uttar Pradesh, India

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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 TNFα, 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-α[4], interleukin (IL)-6, IL-1β, CCL2 and others[5,6] 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

*Correspondent author
Email: k.d.yadav1983@gmail.com

Table 1—Showing classical and proprietary formulation for obesity having *Haridra*

Name of formulation	Composition	Reference/ Name of pharmaceutical company
Karshan and Lekhaniya *Gana*	*Haridra (Curcuma longa), Daru haridra (Berberis aristata), Chitrak (Plumbago zeylanica), Vacha (Acorus calamus)*	*Charak, Sutra Sthan* 4/3
As General formula	*Haridra (C. longa), Pippali (Piper longum), Kutaki (Picrorhiza Kurroa), Shigru (Moringa Oleifera)*	*Astang Hriday Sutra Sthan* 14/21-24
Vyosadi saktu	*Pippali (P. longum), Haridra (C. longa), Haritaki (Terminalia Chebula),Chitrak (P. zeylanica)*	*Chakradatt* 36/10-15
Triphaladi taila	*Haritaki (T. Chebula), Haridra (C. longa), Chitrak (P. zeylanica), Vasa (Adhatoda vasica), herbs*	*Chakradatt 36/30-32*
Vyosadi yoga	*Pippali (P. longum), Haridra (C. longa), Shigru (M. Oleifera),*	*Vrinda madhav 36/10-15*
Harital prayog	*Hartal, Haridra (C. longa),*	*Chakradatt 36/36*
Obex	*Haridra (C. longa), Shilajeet, Guggul (Commiphora mukul), Chitrak (P. zeylanica)*	Arya Aushadhi Pharmaceuticals Works, Indore India. http:// aryaaushadhi indore.com/ ?page_id=27 &single_ prod_id=183
Slim care	*Haridra (C. longa), Haritaki (T. Chebula), Vidanga (Emblica ribs)*	Ayurvedaforall III/540D, Anaril, Thrikunnapuzha, Alappuzha, 690515 Kerala, India http://www.ayurvedaforall. com/1188/slimcare-capsules. html
Lipovedic	*Haridra (C. longa), Guggul (Commiphora mukul), Musta (Cyprus rotundus), pippali (P. longum)*	Vedic Bio labs No. 31, first main road, First Cross Road, Girinagar, Bangalore - 560 085, Karnataka, India http:// www.vedicbiolabs.com/
Haridra	*Haridra (C. longa)*	Morpheme Remedies Pvt Ltd. 296, Industrial Area, Phase 2, Panchkula – 134113, Haryana https://www.morphemeremedies. com/product/turmeric-curcuma-longa/

pharmacological properties *C. longa* shows beneficial effect in management of obesity, diabetes, etc. and in the present review, possible mechanism by which *C. longa* is supportive in management of obesity has been discussed.

Mechanism of *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[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[18]. *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 *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 *C. longa* on their metabolism.

Effect on carbohydrate metabolism

Weight gain is associated with carbohydrate intake[19,20]. Insulin decreases blood glucose levels by suppressing hepatic glucose production, increasing glucose uptake into muscle and increasing adipose 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)[21,22] enhances insulin sensitivity and glucose tolerance[23]. It has been reported that curcumin increases glucose uptake by skeletal muscle mediated by improving the expressions of GLUT4 through the PLC-PI3K pathway[24]. 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[25] is an imperative risk factor for diabetes and cardiovascular disease[26]. The alteration in lipid metabolism may arise due to imbalance between fatty acid synthesis, uptake and β-oxidation[27], i.e. imbalance between adipogenesis and lipolysis**.** Adipogenesis is a differentiation process by which undifferentiated pre-adipocytes are converted to mature adipocytes[28]. During this, SREBP-1c stimulates the expression of C/EBPa, PPAR-g 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[29,30]. Lipolysis is the key process of triglyceride breakdown, which is ultimately converted in to energy through β-oxidation that may be helpful for achieving weight loss[31] 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[32]. It is reported that ethanolic extract of *C. longa* decrease 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[33]. 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[34]. 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[35-37] but serum level of adiponectin is negatively correlated with BMI, waist to hip ratio as well as obesity[38,39]. 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[40], which strongly enhances adiponectin expression (two fold) and secretion (three fold)[41]. 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[42]. 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[43]. Due to this initiation adipose tissue secretes adipokinines like tumour necrosis factor-α (TNF- α), IL-6, etc.[44-46]. TNF-α increases systemic insulin resistance by promoting release of fatty acid from adipose tissue in to blood vessels[47,48] and IL-6 increases lipolysis, fat oxidation in human[49] causing further insulin resistance[50]. Curcumin down regulate expression of various pro-inflammatory cytokines including TNF-α, interleukins by inactivation of the nuclear factor-kappa B (NF-kB)[51], 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[52]. 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[53]. *C. longa* inhibit adipocyte differentiation in dose dependent manner and also alter the expression of genes involved in the adipogenesis[54]. 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 meditors[55,56] and inhibit enzymes such as lipoprotein lipase[57] 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[58-60]. 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[61]. Curcumin, the major component of *C. longa* reduces HIF-1α protein concentration by 70 %[62,63]. 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[64]. 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[65]. Obesity is associated with increased oxidative stress at the level of adipocyte mitochondria because processing of excess free fatty acids causes mitochondrial uncoupling, increasing the release of ROS[66]. When caloric intake exceeds energy expenditure, the substrate-induced increase in Kreb's cycle activity generates an excess of ROS[67]. 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[68]. Antioxidants also act as a replicable or recyclable "buffer" to absorb oxidative hits and excess energy[69]. Furthermore**,** curcumin also enhances the activity of many antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase (GPx)[70] and heme oxygenase-1 (OH-1)[71], 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[72] is related to various human diseases like obesity[73]. FAS inhibitors reduce food intake and body weight[74,75]. 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[76] and produces hypolipedemia[77] 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[78,79], which inhibits FAS, stimulates carnitine palmitoyltransferase-1 (CPT-1) and β -oxidation of fatty acids[80,81], i.e. it helps in reduction of body weight. Curcumin activated AMPK[82] 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[83]. It has been estimated that heritability of body mass index is between 40–70 % in children and adults[84-86] and other anthropometric measures of obesity and regional fat distribution (Skin fold thickness, waist circumference and waist : hip ratio) show similar heritability[87-91]. 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[92] and augmented lipogenic gene expression may also contribute to the development of obesity[93,94]. It is reported that Curcumin repress SREBP-1c and ChREBP expression with repression of L-PK, which down regulate the activity of lipogeneic gene expression and by doing this curcumin prevents obesity and its associated metabolic defects[95]. Furthermore, the overexpression of ob-gene may increase the adipocyte, which ultimately causes obesity through anti-inflammatory, oxidative stress and dysregulation of leptin, insulin and adiponectin[96]. Curcumin also suppresses the Ob-R gene expression[97]. Thus *C. longa* may be beneficial for reduction of obesity by modulating the activity of Egr-1 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 adinopectin concentration, maintains harmony of nutritional substances, influences genetic point and hence may be beneficial for the management of obesity.

References

1 Roberts D L, Dive C and Renehan A G, Biological mechanisms linking obesity and cancer risk: New perspectives, *Annu Rev Med*, 2010, **61**, 301–316.

2 Hotamisligil G S, Inflammation and metabolic disorders, *Nature* 2006, **444**, 860–867.

3 Margaret F G and Gokhan S H, Inflammatory mechanisms in obesity, *Annu Rev Immunol*, 2011, **29**, 415-445.

4 Hotamisligil G S, Arner P, Caro J F, Atkinson R L and Spiegelman B M, Increased adipose tissue expression of tumor necrosis factor-α in human obesity and insulin resistance, *J Clin Investig,* 1995, **95**, 2409–2415.

5 Shoelson S, Lee J and Goldfine A, Inflammation and insulin resistance, *J Clin Investig,* 2006, **116**, 1793–1801.

6 Berg A H and Scherer P E, Adipose tissue, inflammation, and cardiovascular disease, *Circ Res*, 2005, **96**, 939–949.

7 Cai D, Yuan M, Frantz D F, Melendez P A, Hansen L, Jongsoon L, *et al*., Local and systemic insulin resistance resulting from hepatic activation of IKK-βand NF-κB, *Nat Med*, 2005, **11**, 183–190.

8 Ehses J A, Perren A, Eppler E, Ribaux P, Pospisilik J A, Maor-Cahn R, *et al*., Increased number of islet-associated macrophages in type 2 diabetes, *Diabetes* 2007, **56**, 2356–2370.

9 Saghizadeh M, Ong J M, Garvey W T, Henry R R and Kern P A, The expression of TNF α by human muscle. Relationship to insulin resistance, *J Clin Investig*, 1996, **97**, 1111–1116.

10 Friedman J M, Obesity in the new millennium. *Nature* 2000, **404**, 632–634.

11 Willam F G, Central regulation of visceral function. Review of medical physiology, Mac Graw-Hill, New York, 2003, 236–254.

12 Shrivastava N, Lakhan R and Mittal B, Pathophysiology and genetics of obesity*, Indian J Exp Biol* 2007, **45**, 929-936.

13 Schmidt B M, Ribnicky D M, Lipsky P E and Raskin I, Revisiting the ancient concept of botanical therapeutics, *Nat Chem Biol*, 2007, **3**(7), 360–366.

14 Ammon H P T and Wahl M A, Pharmacology of *Curcuma longa*, *Planta Med*, 1991, **57**, 1–7.

15 Vagbhatt and Gupta K A, Astang hridayam vidyotini hindi commentary Sutra Sthan, Chaukhambha Prakashan, Varanasi, 2012, 137.

16 Chattopadhyay I K, Biswas U B and Banerjee R K, Turmeric and Curcumin: Biological actions and medicinal applications, *Curr Sci,* 2004, **87**, 44-53.

17 Barlow S E, the Expert Committee, Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: Summary report, *Pediatrics,* 2007, **120**, 164-192.

18 Bathrellou E, Yannakoulia M, Papanikolaou K, Pehlivanidis A, Pervanidou P, Kanaka, *et al*., Development of a multi-disciplinary intervention for the treatment of childhood obesity based on cognitive behavioural therapy, *Child Fam Behav The,* 2010, **32**, 34-50.

19 Ma Y, Olendzki B, Chiriboga D, Hebert J R, Li Y, Li W, *et al*., Association between dietary carbohydrates and body weight, *Am J Epidemiol*, 2005, **161**, 359–67.

20 Sartorius B, Sartorius K, Aldous C, Madiba T E, Stefan C and Noakes T, Carbohydrate intake, obesity, metabolic syndrome and cancer risk? A two-part systematic review and metaanalysis protocol to estimate attributability, *BMJ Open*, 2016, 6:e009301.

21 Shepherd P R, Gnudi L, Tozzo E, Yang H, Leach F and Kahn B B, Adipose cell hyperplasia and enhanced glucose disposal in transgenic mice overexpressing GLUT4 selectively in adipose tissue, *J Biol Chem,* 1993, **268**, 22243-22246.

22 Singla P, Bardoloi A and Parkash A A, Metabolic effects of obesity: A review, *World J Diabetes,* 2010, **1**(3), 76-88.

23 Shepherd P R and Kahn B B, Glucose transporters and insulin action--implications for insulin resistance and diabetes mellitus, *N Engl J Med*, 1999, **341**, 248-257.

24 Ali M, Mohammad B, Gilda E and Javad M A, The effect of curcumin on GLUT4 gene expression as a diabetic resistance marker in C2C12 Myoblast Cells, *Iranian J Diab Obes*, 2014, **6**(2), 98-104.

25 Virtanen K A, Iozzo P, Hällsten K, Huupponen R, Parkkola R, Janatuinen T, *et al*., Increased fat mass compensates for insulin resistance in abdominal obesity and type 2 diabetes: A positron-emitting tomography study, *Diabetes*, 2005, **54**(9), 2720-6.

26 Abu-Elheiga L, Matzuk M M, Abo-Hashema K A and Wakil S J, Continuous fatty acid oxidation and reduced fat storage in mice lacking acetyl-CoA carboxylase, *Sci,* 2001, **291**, 2613–16.

27 Fruhbeck G, Gomez-Ambrosi J, Muruzabal F J and Burrell M A, The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation, *Am J Physiol Endocrinol Metab*, 2001, **280**, 827-47.

28 Ntambi J M and Young-Cheul K, Adipocyte differentiation and gene expression, *J Nutr,* 2000, **130**, 3122-3126.

29 Darlington G J, Ross S E and MacDougald O A, The role of C/EBP genes in adipocyte differentiation, *J Biol Chem,* 1998, **273**, 30057-60.

30 Duncan R E, Ahmadian M, Jaworski K, Sarkadi-Nagy E and Sul H S, Regulation of lipolysis in adipocytes, *Annu Rev Nutr*, 2007, **27**, 79-101.

31 Gaidhu M P, Anthony N M, Patel P, Hawke T J and Ceddia R B, Dysregulation of lipolysis and lipid metabolism in visceral and subcutaneous adipocytes by high-fat diet: Role of ATGL, HSL, and AMPK, *Am J Physiol Cell Physiol,* 2010, **298**, 961-71.

32 Kim J H, Kim O K, Yoon H G, Park J, You Y, Kim K, *et al*., Anti-obesity effect of extract from fermented *Curcuma longa* L. through regulation of adipogenesis and lipolysis pathway in high-fat diet-induced obese rats, *Food Nutr Res,* 2016, **60**, 30428.

33 Harwood H J, The adipocyte as an endocrine organ in the regulation of metabolic homeostasis, *Neuropharmacol*, 2012, **63**(1), 57-75.

34 Prieur X, Tung YC, Griffin J L, Farooqi I S, O'Rahilly S and Coll A P, Leptin regulates peripheral lipid metabolism primarily through central effects on food intake, *Endocrinol*, 2008, **149**, 5432–5439.

35 Valle M, Gascón F, Martos R, Bermudo F, Ceballos P and Suanes A, Relationship between high plasma leptin concentrations and metabolic syndrome in obese pre-pubertal children, *Int J Obes Metb Disord*, 2003, **27**(1), 13–18

36 Yang W S, Lee W J, Funahashi T, Tanaka S, Matsuzawa Y, Chao C L, *et al*., Plasma adiponectin levels in overweight and obese Asians, *Obes Res*, 2002, **10**, 1104-1110.

37 Mamaghani F, Zarghami N, Maleki M J, Pourhassan-Moghaddam M and Hosseinpanah, Variation of adiponectin levels in normal and obese subjects: Possible correlation with lipid profiles, *Int J Endocrinol Metab* 2009, **3**, 170-117.

38 Hyung-Jin P, Sang-Eun L, Jung-Hyun O, Kyoung-Won S and Kun-Ho S, Leptin, adiponectin and serotonin levels in lean and obese dogs, *BMC Vet Res,* 2014, **10**, 113.

39 Kwon-Il S, Myung-Sook C, Un J J, Hye-Jin K, Jiyoung Y, Seon-Min J and Mi-Kyung L, Effect of curcumin supplementation on blood glucose, plasma insulin, and glucose homeostasis related enzyme activities in diabetic db/db mice, *Mol Nutr Food Res*, **52**, 995–1004.

40 Hajri T, Yao H, Wattacheril J and Marks-Shulman P, Regulation of adiponectin production by Insulin: interaction with tumor necrosis factor a and interlukin 6, *Am J Physiol Endocrinol Metab,* 2011, **300**, 350-360

41 Best L, Elliott A C and Brown P D, Curcumin induces electrical activity in rat pancreatic beta-cells by activating the volume-regulated anion channel, *Biochem Pharmacol*, 2007, **73**, 1768–1775.

42 Roberts D L, Dive C and Renehan A G, Biological mechanisms linking obesity and cancer risk: new perspectives, *Annu Rev Med*, 2010, **61**, 301-316.

43 Wang P, Mariman E, Renes J and Keijer J, The secretory function of adipocytes in the physiology of white adipose tissue, *J Cell Physiol*, 2008, **216**, 13-15.

44 Scherer P E, Adipose tissue: from lipid storage compartment to endocrine organ, *Diabetes*, 2006, **55**, 1537–1545.

45 Halberg N, Wernstedt-Asterholm I and Scherer P E, The adipocyte as an endocrine cell, *Endocrinol Metab Clin N Am*, 2008, **37**, 753–768.

46 Zhang H H, Halbleib M, Ahmad F, Manganiello V C and Greenberg A S, Tumour necrosis factor-alpha stimulates lipolysis in differentiated human adipocytes through activation of extracellular signal-related kinase and elevation of intracellular cAMP, *Diabetes*, 2002, **51**, 2929–2935.

47 Souza S C, Palmer H J, Kang Y H, Yamamoto M T, Muliro K V, Paulson K E, *et al*., TNF-alpha induction of lipolysis is mediated through activation of the extracellular signal related kinase pathway in 3T3–L1 adipocytes, *J Cell Biochem*, 2003, **89**(6), 1077–1086.

48 Van Hall G, Steensberg A, Sacchetti M, Fischer C, Keller C, Schjerling P, *et al*., Interleukin-6 stimulates lipolysis and fat oxidation in humans, *J Clin Endocrinol Metab,* 2003, **88**(7), 3005–3010.

49 Kern P A, Ranganathan S, Li C, Wood L and Ranganathan G, Adipose tissue tumour necrosis factor and interleukin-6 expression in human obesity and insulin resistance, *Am J Physiol Endocrinol Metab*, 2001, **280**, 745–751.

50 Yoysungnoen P, Wirachwong P, Bhattarakosol P, Niimi H and Patumraj S, Effects of curcumin on tumor angiogenesis and biomarkers, COX-2 and VEGF, in hepatocellular carcinoma cell-implanted nude mice, *Clin Hemorheol Microcirc*, 2006, **34**,109–115.

51 Koerner A, Kratzsch J and Kiess W, Adipocytokines: leptin the classical, resistin the controversial, adiponectin– the promising, and more to come, *Best Pract Res Clin Endocrinol Metab,* 2005, **19**, 525–546.

52 Arumughan M, Vijayan P, Raghu C, Ashok G, Dhanraj S A, Kumarappan C T, Anti-adipogenic activity of *Capsicum annum* (Solanaceae) in 3T3 L1, *J Compl Int Med*, 2008, **5**(1), 1-9.

53 Prathapan A, Krishna M S, Lekshmi P C, Raghu K G and Menon A N, Modulation of adipogenesis and glucose uptake by *Curcuma longa* extract in 3T3L1 and L6 cell lines - An in vitro study, *Asian Pac J Trop Dis*, 2012, **2**(S1), S163-S165

54 O'Rourke R W, White A E, Metcalf M D, Olivas A S, Mitra P, Larison W G, *et al*., Hypoxia induced inflammatory cytokine secretion in human adipose tissue stromovascular cells, *Diabetologia*, 2011, **54**(6), 1480–1490.

55 Famulla S, Schlich R, Sell H, and Eckel J, Differentiation of human adipocytes at physiological oxygen levels results in increased adiponectin secretion and isoproterenol-stimulated lipolysis, *Adipocyte*, 2014, **1**(3), 132–181.

56 Yao Q, Shin M K and Jun J C, Effect of chronic intermittent hypoxia on triglyceride uptake in different tissues, *J Lipid Res*, 2013, **54**(4), 1058–1065.

57 Huang X, He Z, Jiang X, Hou M, Tang Z, Zhen X, *et al*., Folic acid represses hypoxia-induced inflammation in THP-1 cells through inhibition of the PI3K/Akt/HIF-1α pathway, PLoS One, 2016, **11**(3), e0151553.

58 Priyanka A, Anusree S S, Nisha V M and Raghu K G, Curcumin improves hypoxia induced dysfunctions in 3T3-L1 adipocytes by protecting mitochondria and down regulating inflammation, *Biofactors,* 2014, **40**(5), 513-23.

59 Mackenzie R W A and Watt P, A Molecular and whole body insight of the mechanisms surrounding glucose disposal and insulin resistance with hypoxic treatment in skeletal muscle, *J Diabetes Res,* 2016, **2016**, 10.

60 Goel A, Kunnumakkara A B and Aggarwal B B, Curcumin as "Curecumin": From kitchen to clinic, *Biochem Pharmacol,* 2008, **75**(4), 787–809.

61 Wanxing D, Yuanhong C, Rong L, Qinhong X, Jianjun L, Caiqiao Y, *et al*., Curcumin inhibits hypoxia inducible factor-1α-induced epithelial-mesenchymal transition in HepG2 hepatocellular carcinoma cells, *Mol Med Rep,* 2014, **10**, 2505-2510.

62 Hyunsung C, Yang-Sook C, Seung-Won K, Myung-Suk K, and Jong-Wan P, Curcumin inhibits hypoxia-inducible factor-1 by degrading aryl hydrocarbon receptor nuclear translocator: A mechanism of tumor growth inhibition, *Mol Pharmacol*, 2006, **70**, 1664–1671.

63 Septembre-Malaterre A, Le Sage F, Hatia S, Catan A, Janci L and Gonthier M P, Curcuma longa polyphenols improve insulin-mediated lipid accumulation and attenuate proinflammatory response of 3T3-L1 adipose cells during oxidative stress through regulation of key adipokines and antioxidant enzymes, *Biofactors*, 2016, **20**. doi: 10.1002/biof.1288. [Epub ahead of print]

64 Horvath T L, Andrews Z B and Diano S, Fuel utilization by hypothalamic neurons: Roles for ROS, *Trends Endocrinol Metab*, 2009, **20**, 78–87.

65 Fenster C P, Weinsier R L, Darley-Usmar V M and Patel R P, Obesity, aerobic exercise, and vascular disease: The role of oxidant stress, *Obes Res*, 2002, **10**(9), 964-968.

66 Maddux B A, See W, Lawrence J C J, Goldfine A L, Goldfine I D and Evans J L, Protection against oxidative stress-induced insulin resistance in rat L6 muscle cells by micromolar concentrations of -lipoic acid, *Diabetes*, 2001, **50**, 404–410.

67 Jain S K, Rains J and Jones K, Effect of curcumin on protein glycosylation, lipid peroxidation, and oxygen radical generation in human red blood cells exposed to high glucose levels, *Free Radic Biol Med,* 2006, **41**, 92-96.

68 Halliwell B and Gutteridge J M C, Antioxidant defences, *In*: Free radicals in biology and medicine, 3rd Edn, Oxford University Press, Oxford, 1999, 105–245.

69 Jaydip B, Soumi R, Sutapa M, Dona S, Madhumita R, Indian spice curcumin may be an effective strategy to combat the genotoxicity of arsenic in swiss albino mice, *Asian Pacific J Cancer Prev*, 2009, **11**, 239-246.

70 Jeong G S, Oh G S, Pae H O, Jeong S O, Kim Y C *et al.*, Comparative effects of curcuminoids on endothelial heme oxygenase-1 expression: Ortho-methoxy groups are essential to enhance heme oxygenase activity and protection, *Exp Mol Med*, 2006, **38**, 393–400.

71 Smith S, The animal fatty acid synthase: one gene, one polypeptide, seven enzymes, *FASEB J,* 1994, **8**, 1248-1259.

72 Lin J K and Lin-Shiau S Y, Mechanism of hypolipidemic and anti-obesity effects of tea and tea polyphenols, *Mol Nutr Food Res*, 2006, **50**, 211-217.

73 Loftus T M, Jaworsky D E, Frehywot G L, Townsent C A, Ronjnett G V, Lane D M *et al*., Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors, *Science*, 2000, **288**, 2379–2381.

74 Richard S S, Fatty acid synthase inhibitors reduce food intake and body weight, *Pediatr Res* 2000, **48**, 422–422.

75 Wang S and Peng D, Regulation of adipocyte autophagy- The potential anti-obesity mechanism of high density lipoprotein and apolipoprotein A-I, *Lipids Health Dis,* 2012, **11**, 131.

76 Paul B L, Yukio F, Mortensen R and Hashimoto T, Identification and oxidation enzymes among peroxisomal polypeptides increase in coomassie blue-stainable protein after clofibrate treatment, *FEBS Letters*, 1982, **150**, 307-310.

77 Hardie D G and Carling D, The AMP-activated protein kinase F fuel gauge of the mammalian cell? *Eur J Biochem*, 1997, **246**, 259–273.

78 Kemp B E, Stapleton D, Campbell D J, Chen Z P, Murthy S, Walter M *et al*., AMP-activated protein kinase, super metabolic regulator, *Biochem Soc Trans*, 2003, **31**, 162–168

79 Landree L E, Hanlon A L, Strong D W, Rumbaugh G, Miller I M, Thupari J N *et al*., C75, a fatty acid synthase inhibitor, modulates AMP-activated protein kinase to alter neuronal energy metabolism, *J Biol Chem*, 2004, **279**, 3817-3827.

80 Thupari J N, Landree L E, Ronnett G V and Kuhajda F P, C75 increases peripheral energy utilization and fatty acid oxidation in diet induced obesity, *Proc Natl Acad Sci*, 2002, **99**, 9498–9502

81 Um M Y, Hwang K H, Ahn J and Ha T Y, Curcumin attenuates diet-induced hepatic steatosis by activating AMP-activated protein kinase, *Basic Clin Pharmacol Toxicol,* 2013, **113**, 152-157.

82 Cummings D E and Schwartz W, Genetics and pathophysiology of human obesity, *Annu Rev Med,* 2003, **54**, 453-471.

83 Stunkard A J, Foch T T and Hrubec Z, A twin study of human obesity, *JAMA*, 1986, **256**, 51–54.

84 Turula M, Kaprio J, Rissanen A and Koskenvuo M, Body weight in the finish twin cohort, Diabetes, *Res Clin Pract,* 1990, **10**, 33-36.

85 Wardle J, Carnell S, Haworth C M and Plomin R, Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment, *Am J Clin Nutr*, 2008, **87**, 398–404.

86 Malis C, Rasmussen E L, Poulsen P, Petersen I, Christensen K, Beck-Nielsen H *et al*., Total and regional fat distribution is strongly influenced by genetic factors in young and elderly twins, *Obes Res*, 2005, **13**(12), 2139–2145.

87 Moll P P, Burns T L and Lauer R M, The genetic and environmental sources of body mass index variability: the muscatine ponderosity family study, *Am J Hum Genet*, 1991, **49**, 1243–1255.

88 Rose K M, Newman B, Mayer-Davis E J and Selby J V, Genetic and behavioural determinants of waist–hip ratio and waist circumference in women twins, *Obes Res*, 1998, **6**, 383–392.

89 Selby J V, Newman B, Quesenberry Jr C P, Fabsitz R R, King M C and Meaney F J, Evidence of genetic influence on central body fat in middle-aged twins, *Hum Biol*, 1989, **61**, 179–194.

90 Stunkard A J, Sørensen T I, Hanis C, Teasdale T W, Chakraborty R, Schull W J and Schulsinger F, An adoption study of human obesity, *N Engl J Med*, 1986, **314**, 193–198.

91 Uyeda K and Repa J J, Carbohydrate response element binding protein, ChREBP, a transcription factor coupling hepatic glucose utilization and lipid synthesis, *Cell Metab,* 2006, **4**, 107–110.

92 Dentin R, Benhamed F, Hainault I, Fauveau V, Foufelle F, *et al.*, Liver specific inhibition of ChREBP improves hepatic steatosis and insulin resistance in ob/ob mice, *Diabetes*, 2006, **55**, 2159–2170.

93 Xu F, Gao Z, Zhang J, Rivera C A, Yin J, Weng J and Ye J, Lack of SIRT1 (Mammalian Sirtuin 1) activity leads to liver steatosis in the SIRT1+/- mice: a role of lipid mobilization and inflammation, *Endocrinol*, 2010, **151**, 2504–2514.
94 Shao W, Yu Z, Chiang Y, Yang Y, Chai T, Foltz W, Lu H, Fantus I G and Jin T, Curcumin prevents high fat diet induced insulin resistance and obesity via attenuating lipogenesis in liver and inflammatory pathway in adipocytes, *PLos One,* 2012, **7**(1), e28784.
95 Fredrik L, Peter A, Louise N and Martin S, Overexpression of the obese (ob) gene in adipose tissue of human obese subjects, *Nat Med* 1995, **1**, 950–953.
96 Youcai T, Shizhong Z, and Anping C, Curcumin eliminates leptin's effects on hepatic stellate cell activation via interrupting leptin signaling, *Endocrinol,* 2009, **150**(7), 3011–3020.
97 Kazem N K, Abolfazl A, and Mohammad P M, Curcumin inhibits leptin gene expression and secretion in breast cancer cells by estrogen receptors, *Cancer Cell Int*, 2014, **14**, 66.