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RESEARCH ARTICLE

GAMMA ORYZANOL-A THERAPEUTIC AGENT.

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Abstract

Gamma oryzanol is a combination of ferulate, esters of fatty acid and triterpene alcohol which acts as an antioxidant against free radicals. It is present in rice bran oil however it also occurs in corn and barley oils. It also possesses several properties which play an important role in lowering plasma and serum cholesterol by decreasing its absorption to the blood from intestinal tract, alleviate postmenopausal syndrome, improve insulin sensitivity, reduce the skin related problems and growth of cancerous cells. It also increases testosterone levels, thus stimulate secretion of endorphins and also promote the growth of lean muscle tissue, hence find applications in body building aid and health supplements for athletes or sport persons. It also stimulates immune system. It is widely used in cosmoceutical, nutraceutical and pharmaceutical products due to all these health related properties.

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Introduction and composition:

Gamma oryzanol is the term which is used to refer to a collection of molecules with 4, 4-dimethylsterol or 4-desmethylenesterol groups esterified to the ferulic acid build on a ferulic acid backbone. In other words, it is a mixture of steryl ferulates, which are formed by esterification of the hydroxyl group of sterols (β -sitosterol, campesterol, stigmasterol) or triterpene alcohols (cycloartenol, cycloartanol, cyclobranol, 24-methylenecycloartanol) with the carboxylic acid group of ferulic acid (Bucci et al., 2003; Yu et al., 2007; Imsanguan et al., 2008; Lu et al., 2011; Jeng et al., 2012). The compounds which contain double bond between C₅ and C₆ or between C₇ and C₈ are referred to as sterols while sterols which having a saturated steroid skeleton are called stanols (Akihisa et al., 2000; Deepam et al., 2011; Mandak and Nystrom, 2012). Gamma oryzanol commonly referred to the compounds include such as:

- β -Sitosterol (Common in many plants) (Fang et al., 2003).
- Campesterol (Fang et al., 2003).
- Cycloartenyl ferulate and Cycloartenol, the first of which is seen as the primary ingredients (Fang et al., 2003).
- 24-methylenecycloartenol (Fang et al., 2003).

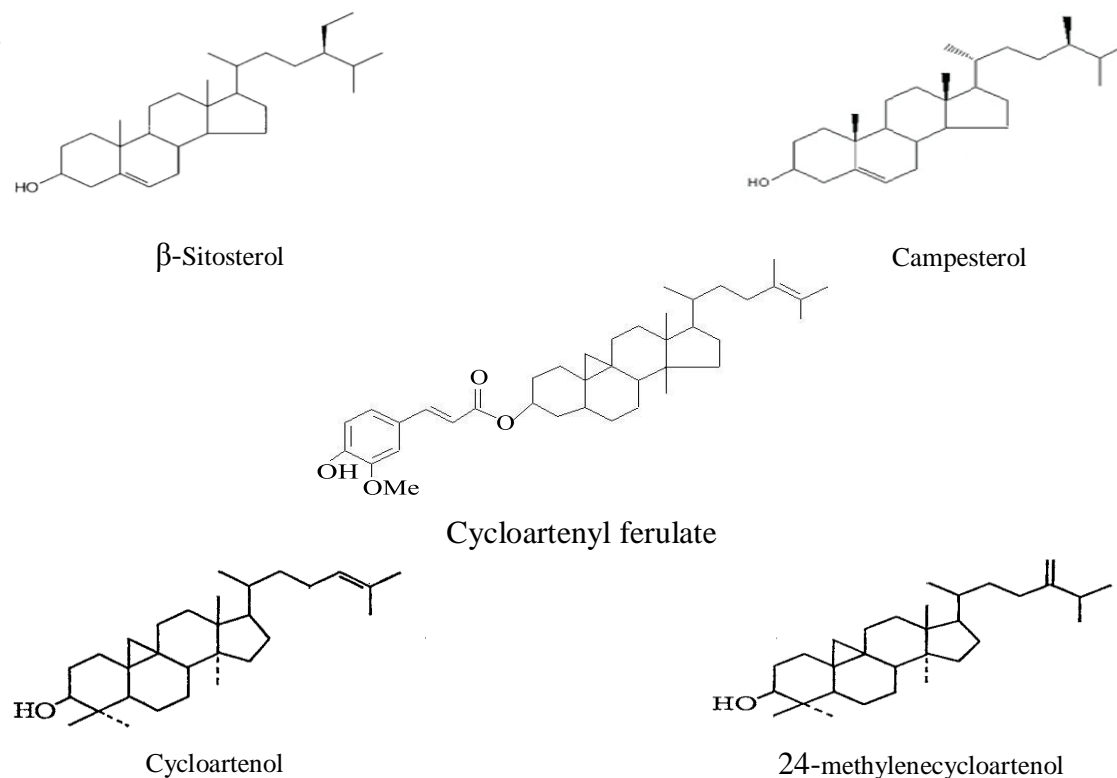


Fig. 1: Chemical Structure of Major Components of γ -Oryzanol (Thompson and Grundy, 2005; Xu et al., 2001; Goad and Godwin, 1967)

At least 25 components of gamma oryzanol have been identified on the basis of their absorbance maxima at 330 nm, in which 5 components are major constituting about 95% of the total gamma oryzanol content (Akihisa et al. 2000; Xu et al. 2001; Fang et al. 2003; Miller and Engel 2006). These 5 gamma oryzanol components contribute to the total gamma oryzanol content is in the following increasing order: stigmasteryl trans-ferulate (present at 1-7 % of the total), β -sitosteryl trans-ferulate (7-17 %), campesteryl trans-ferulate (15-23 %), cycloartenyl trans-ferulate (19-26 %) and 24-methylenecycloartanyl trans-ferulate (34-44 %). β -sitostanyl trans-ferulate, β -sitosteryl cis-ferulate, campestanyl trans-ferulate, cycloartenyl cis-ferulate, cycloart-23Z-ene-3 β ,25-diol-3 β -trans-ferulate, cycloeucaleanol trans-ferulate, D7-campestanyl trans-ferulate, D7-campestenyl trans-ferulate, D7-sitostenyl trans-ferulate, D7-stigmastanyl trans-ferulate, hydroxylated cycloartenol trans-ferulate, 24-methylenecholesterol trans-ferulate, 24-hydroxy-24-mythylcycloartanol trans-ferulate, 24-methylenecycloartanyl cis-ferulate, 24-methylcholesterol trans-ferulate, 24-methylenecholesterol cis-ferulate, 25-hydroxy-24-mythylcycloartanol trans-ferulate, stigmastanyl cis-ferulate, stigmastanyl trans-ferulate, (24R)-cycloart-25-ene-3 β ,24-diol-3 β -trans-ferulate and (24S)-cycloart-25-ene-3 β ,24-diol-3 β -trans-ferulate are the other components of gamma oryzanol (Akihisa et al., 2000; Diack and Sask, 1994; Fang et al., 2003 and Xu et al. 2001).

The content of gamma oryzanol varied, but tends to be 244.1-342.6 mg/Kg with most content contributed to Cycloartenyl ferulate (27-30%) and 24-methylenecycloartenyl ferulate (53-57%) depending on the strain of rice (Zubair et al., 2012). Gamma oryzanol is a compound which possesses antioxidative property besides, it also decreases plasma cholesterol (Yoshino et al., 1989), lowering serum cholesterol (Gerhardt et al., 1998), decreasing cholesterol absorption (Gerhardt et al., 1998) and decreasing platelet aggregation (Seetharamaiah et al., 1990). It also helps in the treatment of hyperlipidemia (Nakayama et al., 1987), post-menopausal syndrome (Murase and Iishima, 1982) and to increase the muscle mass (Bonner et al., 1990).

Therapeutic roles of gamma oryzanol:-

Due to its unique composition and nutritional properties, gamma oryzanol finds many roles in different health conditions. These are:

- **Role in Immunity:** The Nuclear Factor kappa-light-chain-enhancer of activated β -cells (NF- κ B) translocation in lipopolysaccharide-stimulated (LPS) macrophages was prevented at a 10ng/ml concentration by gamma oryzanol (specifically β -sitosterol ferulate, Cycloartenyl ferulate and 24-methylenecycloartenyl ferulate). The translocation of NF- κ B was reduced to below 20% by gamma oryzanol with cycloartenyl ferulate at 10ng/ml and with other components between 20-40 % (Islam et al., 2009). This inhibition has also been seen in endothelial cells, the LPS-induced NF- κ B translocation was reduced at 30 μ M gamma oryzanol to 12.5%, compared to Pyrrolidine dithiocarbamate (PDTC) (Sakai et al., 2012). In a study of rats with implanted colonic tumors, an increase by 130%, 170% and 220% in NK cell activity above control by feeding orally either 0.2, 0.5 or 1 % gamma oryzanol for two weeks while evaluating splenic natural killer (NK) cell activity (Kim et al., 2012). At oral doses of 0.2, 0.5, or 1% of the diet containing gamma oryzanol for 2 weeks was able to increase the activity of macrophages that suppressed by the presence of a colonic tumor. The activity seen in tumor planted mice (50% or so) was increased to 80% of control by 1% of diet (when nitric oxide release while evaluating) and phagocytosis normalization (Kim et al., 2012). This was accomplished by preservation of IL-1b, IL-6 and TNF- α (Kim et al., 2012).
- **Role in Hyperlipidemia:** The cholesterol and triglyceride lowering (hypolipidemic) effects were observed in gamma oryzanol by increasing the conversion of cholesterol to bile acids; it also increases the excretion of bile acids and inhibits the absorption of cholesterol to the blood from the intestinal tract. The various clinical trials revealed that in subjects with elevated lipid levels, 300 mg of gamma oryzanol supplementation per day can lower 8-12 % cholesterol and approximately 15% triglycerides (Murray, 1996; Fujiwara et al., 1982; Yamauchi et al., 1981). In rats study, diet containing gamma oryzanol at 0.5% increased the amount of bile acids and sterols by 246% and 107% respectively in the feces (Cheng et al., 2010). The absorption of cholesterol was negatively influenced by gamma oryzanol and the micelle formation was also impaired by it at high concentrations (Makynen et al., 2012). *In vitro* study, less inflammatory response was showed by NF- κ B which results in adhesion molecules less expression. At 3 μ M, vascular cell adhesion molecule 1 (VCAM-1) and E-selectin were less expressed but when concentration was increased to 30 μ M, intercellular adhesion molecule 1 (ICAM-1) as well as both of those were reduced; this result in the less monocyte adhesion, decreasing a 7-fold increment under inflammatory conditions to 1.7-fold under the influence of 30 μ M gamma oryzanol and was twice as effective as the Pyrrolidine dithiocarbamate (PDTC) (Sakai et al., 2012). The cholesterol lowering action of gamma oryzanol was studied in hamsters which were made cholesterolemic by feeding chow-based diets (consisting 0.1% cholesterol with or without oryzanol and coconut oil) for 7 weeks. There was a significant reduction in absorption of cholesterol (25%), plasma total cholesterol (28%) and non-high-density lipoprotein cholesterol (34%) in oryzanol fed hamsters compared to control one. There was also a reduction of 67% in aortic fatty streak formation (Rong et al., 1997).
- **Role in Diabetes Mellitus:** The 0.5% gamma oryzanol over 4 weeks in diets of rats reduced the rise in the concentrations of serum glucose which was produced by a high-fat diet and also increased the insulin levels and glycogen carbohydrate content (Son et al., 2011). The suppression of Glucose-6-Phosphatase (G6Pase) and Phosphoenolpyruvate carboxykinase (PEPCK) enzyme activity was associated with Gamma-Oryzanol, and Ferulic Acid at 0.5% also showed same results at similar potency (Son et al., 2011). In a study, feeding of 0.525% gamma oryzanol to a rat group influenced a lesser insulin area under the curve (AUC) but there was no influence on glucose area under the curve (AUC) or response to an intraperitoneal glucose tolerance test by either glucose or insulin (Cheng et al., 2010).
- **Role in Postmenopausal Syndrome:** In menopause, the immature egg cells in the ovaries give less response resulted in FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone) oversecretion by the pituitary, which is responsible to start the another ovulatory cycle which contributes to the onset of hot flashes and menopausal symptoms (profuse sweating, mood changes) (Murray, 1996). The supplementation of 150 mg gamma oryzanol twice daily has been shown to reduce the luteinizing hormone (LH) secretion by the pituitary gland and also promote the release of endorphin by the hypothalamus (Murray, 1996). In clinical trials of menopausal women and women whose ovaries were surgically removed, around 67-85 % women experienced a significant reduction in the symptoms of menopause by treating with gamma oryzanol (Murray, 1996; Fujiwara et al., 1982). During menopause, the decline in circulating estrogen levels lead to the rise in blood cholesterol and the development of atherosclerosis in postmenopausal women. This is due to the fact that cholesterol was not efficiently removed from blood as the number of low density lipoprotein cholesterol receptors on body cells increases by estrogen (Murray, 1996; Fujiwara et al., 1982). Studies on gamma oryzanol in Japan revealed that

it is beneficial in the treatment of menopausal syndromes, elevated cholesterol and various gastrointestinal conditions (Ishihara et al., 1982).

- **Role in Cancer:** The gamma oryzanol was able to regulate angiogenesis, suppressing 61% of blood vessel formation in tumor implanted mice was suppresses at the diet of 1% (Kim et al., 2012). It was also able to reduce melanin concentration by 13% at 3 μ M and 38% at 30 μ M in B16F1 Melanoma cells; as there is a correlation with a reduction in protein kinase A (PKA) activity that reduced melanin synthesis by decreasing microphthalmia-associated transcription factor (MTIF) (Jun et al., 2012). There was also a Tyrosinase protein content and mRNA downregulation (Jun et al., 2012). In a study of rats after implantation of colonic tumor, evaluated the components of rice bran (Gamma Oryzanol, Ferulic Acid, Phytic Acid and Tocotrienols) at 0.2% that tumor size was reduced slightly by all components but gamma oryzanol and somewhat phytic acid was more effective (Kim et al., 2012). The dose-dependent reductions in colonic tumor size at 0.2%, 0.5% and 1% of diet was found in these rats, with 1% reducing the tumor size by 44% yet 10% rice bran (used as an active control) reduced size by 7% (Kim et al., 2012).

- **Role in Interaction with Hormones:-
Testosterone:**

The supercritical carbon extraction of rice bran itself showed to suppress the 5 α reductase type I enzyme (Ruksiriwanich et al., 2011), investigated the increment in the concentrations of testosterone and reduced dihydrotestosterone (DHT) in the body. In healthy male athletes alongwith a weight training program, 500 mg gamma oryzanol was failed to influence the concentrations of testosterone (Fry et al., 1997). Thus, gamma oryzanol do not caused an increment in the concentration of testosterone.

- Cortisol, Estrogen and Growth Hormone:-**

In 22 healthy male athletes, 500 mg of gamma oryzanol daily for 9 weeks constitute with a resistance training program significantly failed to affect the circulating levels of cortisol, estrogen and growth hormone (Fry et al., 1997).

- Adiponectin:-**

Adiponectin, a hormone which is secreted by fat tissue and known as an adipokine that increases insulin sensitivity (Heilbronn et al., 2003); its decrease with obesity is correlated with an increase in insulin resistance (Statnick et al., 2000; Yamauchi et al., 2001). Its oral administration to mice appears to increase adiponectin in circulation, yet incubating an adipocyte (fat cell) with gamma oryzanol fails to induce secretion of adiponectin (Ohara et al., 2009).

In rats study, there was a reduction in the circulating levels of adiponectin with palmitate (a fatty acid) and beef tallow fed to these rats noted that at 0.025 mmol gamma oryzanol was able to preserve adiponectin levels under the influence of palmitate and acted to increase circulating adiponectin in control (corn oil) (Nagasaka et al., 2011). As palmitate activates NF- κ B (Cacicedo et al., 2005) which then acts to suppress adiponectin secretion from mouse 3T3-L1 adipocytes (Ohara et al., 2009) secondary to binding to Peroxisome Proliferator-Activator Receptor Gamma (PPAR γ) and inhibiting its genomic actions (Suzawa et al., 2003), it is possible that these observed effects are secondary to gamma oryzanol inhibiting NF- κ B. It was later confirmed that gamma oryzanol (290mcg/kg) was able to increase adiponectin levels, and alongside Gamma Amino Butyric Acid (GABA) (also found in rice bran, 600mcg/kg) there appeared to be slightly better effects, but did not appear to be significantly synergistic (Ohara et al., 2011). In animals, gamma oryzanol showed to increase adiponectin levels.

- Conclusion:-**

Gamma oryzanol contains several components which are known for their potential role in reducing the risk of cardiovascular disease by controlling blood cholesterol and fat absorption, enhancing insulin sensitivity, reducing cancer risk, alleviating menopausal disorders, providing gastrointestinal health. It also serves as a natural source of antioxidant. Thus, it is known for several applications in cosmoceutical, nutraceutical and pharmaceutical industries.

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