Garlic derivatives: role in obesity and related disorders

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Abstract

Introduction

For centuries, garlic has been used for culinary and remedial purposes. In recent years, plant-based chemicals have been extensively explored for their potential as nutraceuticals in the treatment of various health conditions. Garlic-derived organosulfur compounds with anti-oxidant and anti-inflammatory properties can relate to incredible beneficial effects in treating various cancer conditions in vitro and in vivo models. Some garlic compounds have the potential to inhibit adipocyte proliferation and differentiation, and they reduce their number by apoptosis. Both adipocytes and bone-forming osteoblasts arise from a common precursor, mesenchymal stem cells. Because of this common lineage, there exists a direct relationship between obesity and osteoporosis, especially in post-menopausal females. Garlic and its compounds have proven to be beneficial in reducing adiposity and improving bone health in rodents. This critical review discusses the role of garlic derivatives in obesity and related disorders.

Conclusion

Garlic and its derivatives hold promise in the development of therapeutics to address problems of obesity and associated health conditions.

Introduction

Obesity has assumed alarming proportions, and its incidence is increasing worldwide both in developed and developing countries. According to the latest data from the National Health and Nutrition Examination Survey, more than one-third of adults and almost 17% of youth were obese in the USA in 2009–2010, and the prevalence levels did not differ between adult men (35.5%) and women (35.8%)1. The problem of obesity is compounded by its involvement in a multitude of disorders including, but not limited to insulin resistance, type 2 diabetes, osteoporosis, cardiovascular diseases, cancer, etc. These manifestations are the result of impaired adipose tissue metabolic activity that contributes to altered endocrine function.

The incidence of obesity is due to an increase either in the adipocyte number (hyperplasia) and/or in the volume of a typical adipocyte (hypertrophy)2. Moreover, there is a turnover of fat cells throughout life under different sets of conditions, which may result in obesity. Pharmaceutical remedies formulated to alleviate the problem of obesity, which are currently available, are associated with undesirable side effects. Efforts to explore non-pharmaceutical therapeutic approaches have since grown and much of such focus has been on natural products in general and phytochemicals in particular. Garlic derivatives are one such potential class of phytochemicals that can produce promising results in therapy and are capable of providing a number of other health benefits. A wealth of information is available showing beneficial effects of garlic derivatives such as anti-adipogenic, anti-inflammatory, antioxidant, anti-cancer, antimutagenic, anti-microbial, anti-hyperlipidaemic, anti-viral and other additional properties3–10 (Figure 1). While the therapeutic action of garlic compounds in cancer treatment has generated a lot of interest and research, the anti-adipogenic potential has not been explored much. This critical review explores anti-adipogenic potential of garlic compounds.

Discussion

The author has referenced some of its own studies in this review. The protocol of these studies have been approved by the relevant ethical committee related to our institution in which it was performed.

Garlic compounds: chemistry

Two classes of organosulfur compounds are derived from garlic: (1) lipid-soluble (Figure 2a) and (2) water-soluble (Figure 2b) allyl sulfur compounds. Lipid-soluble sulfur compounds are formed from its parent sulfur compound, alliin, which constitutes about 80% of the cysteine sulphinolides in garlic. Lipid-soluble allyl sulfur compounds such as ajene, diallyl sulphide (DAS), diallyl disulphide (DADS) and diallyl trisulphide (DATS) are released from allin catalysed by allinase enzyme, which is released by either chopping or crushing garlic. Water-soluble allyl sulfur compounds, such as S-allyl cysteine (SAC) and S-allyl mercaptocysteine, are obtained during long-term incubation of crushed garlic in aqueous solutions in the ageing process.

Garlic organosulfur compounds and adipogenesis

Several organosulfur compounds have shown inhibitory effects on adipogenesis11,12. They reduce the synthesis of lipids in 3T3-L1 adipocytes and human adipocytes. In addition to this, some of

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Figure 1: A list of various beneficial effects of garlic and its derivatives.

these compounds are able to decrease cell viability and are implicated in influencing the adipocyte number. Such suppression in adipocyte viability was reportedly caused by ajoene-induced apoptosis. Ajoene is more potent on adipocytes when compared to several other garlic organosulphur compounds; in addition, ajoene significantly suppresses cell viability, adipogenesis and increases apoptosis in different stages of 3T3-L1 adipocytes. However, other garlic compounds, such as DAS, DADS, DATS, deoxyallin and allyl methyl sulphide, have no significant effect on any of the aforementioned parameters at any adipocyte stage. Generation of reactive oxygen species (ROS) and subsequent events of kinase activation (JNK and ERK), degradation of PARP-1 and translocation of apoptosis-inducing factor AIF can be attributed to apoptosis in ajoene-treated 3T3-L1 adipocytes. Similar anti-proliferative and pro-apoptotic properties of ajoene have been the key biological factors for its use with chemotherapeutic drugs, cytarabine and fludarabine, in human CD34-positive resistant myeloid leukaemia cells. Diallyl trisulphide, one of the prominent components in garlic oil, inhibited the differentiation of preadipocytes into lipid-filled adipocytes through prolonged ERK activation, by inhibiting CCAAT/enhancer-binding protein (C/EBPα and γ) and subsequent fatty acid synthase (FAS). Thiacremonone, another organosulphur compound isolated from garlic, has significantly reduced differentiation of 3T3-L1 preadipocytes by down-regulating adipogenesis-related transcription factors and markers; in differentiating cells, acetyl coA-carboxylase1, an essential component in fatty acid synthesis and metabolism, has been lowered through AMPK activation. Inhibition of adipogenesis through abolition of inflammatory molecule secretion (IL-6 and MCP-1) and reduced expression of adipogenic factors genes such as PPARγ, CEBPα, lipoprotein lipase (LPL) and adiponectin by 1,2-vinyl-dithiin in differentiating human preadipocytes is another example to substantiate anti-adipogenic properties of organosulphur compounds of garlic. In contrast, DADS accelerated terminal differentiation of 3T3-L1 cells into adipocytes through inhibiting histone deacetylase, increasing the expression of adipogenesis-related LPL, FAS, SREBP1c, ap2 and PPARγ and lowering the expression of pref-1, a preadipocyte marker.

Structure–activity relationships

Structure–activity relationships are not only critical in explaining the chemical nature and functional relationships of the compounds but are also indicators of the type of activity/reaction that they can elicit in target biological systems. Thiols, sulphur-containing structures, are important components of all biological systems and are essential for life. Organosulphur compounds of garlic have either one or more sulphur atoms, through which they, at least in part, exert their biological activity. In addition to the number of sulphur atoms, types of alk(en)yl groups are activity-determining factors. Although allyl groups appear to induce growth arrest in cancer cells, all allyl compounds are not equally potent. Lipid-soluble allyl sulphur compounds such as DADS and DATS are more effective than water-soluble allyl sulphur compounds such as SAC. The anti-oxidant property of garlic derivatives stems from their ability to scavenge free radicals and offer protection to cellular membrane from various assaults, and at the same time, decrease cell viability and are implicated in influencing the adipocyte number. Such suppression in adipocyte viability was reportedly caused by ajoene-induced apoptosis. Ajoene is more potent on adipocytes when compared to several other garlic organosulphur compounds; in addition, ajoene significantly suppresses cell viability, adipogenesis and increases apoptosis in different stages of 3T3-L1 adipocytes. However, other garlic compounds, such as DAS, DADS, DATS, deoxyallin and allyl methyl sulphide, have no significant effect on any of the aforementioned parameters at any adipocyte stage. Generation of reactive oxygen species (ROS) and subsequent events of kinase activation (JNK and ERK), degradation of PARP-1 and translocation of apoptosis-inducing factor AIF can be attributed to apoptosis in ajoene-treated 3T3-L1 adipocytes. Similar anti-proliferative and pro-apoptotic properties of ajoene have been the key biological factors for its use with chemotherapeutic drugs, cytarabine and fludarabine, in human CD34-positive resistant myeloid leukaemia cells. Diallyl trisulphide, one of the prominent components in garlic oil, inhibited the differentiation of preadipocytes into lipid-filled adipocytes through prolonged ERK activation, by inhibiting CCAAT/enhancer-binding protein (C/EBPα and γ) and subsequent fatty acid synthase (FAS). Thiacremonone, another organosulphur compound isolated from garlic, has significantly reduced differentiation of 3T3-L1 preadipocytes by down-regulating adipogenesis-related transcription factors and markers; in differentiating cells, acetyl coA-carboxylase1, an essential component in fatty acid synthesis and metabolism, has been lowered through AMPK activation. Inhibition of adipogenesis through abolition of inflammatory molecule secretion (IL-6 and MCP-1) and reduced expression of adipogenic factors genes such as PPARγ, CEBPα, lipoprotein lipase (LPL) and adiponectin by 1,2-vinyl-dithiin in differentiating human preadipocytes is another example to substantiate anti-adipogenic properties of organosulphur compounds of garlic. In contrast, DADS accelerated terminal differentiation of 3T3-L1 cells into adipocytes through inhibiting histone deacetylase, increasing the expression of adipogenesis-related LPL, FAS, SREBP1c, ap2 and PPARγ and lowering the expression of pref-1, a preadipocyte marker.

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Garlic derivatives: role in obesity and related disorders

Critical review

Garlic derivatives: in vivo studies

There are certain pharmaceutical formulations and prescription medications that are available for weight loss in markets, but most of these are unsuccessful in reducing obesity and are often associated with some side effects. In this context, phytochemicals and their formulations with their ability to work—either alone or synergistically in combination—have tremendous potential to be developed as alternative therapeutics to treat obesity and other associated diseases.

Various beneficial effects of garlic-derived organosulphur compounds are attributed to their anti-oxidant and anti-cancer properties. These properties of various garlic extracts and compounds have also been favored to show the beneficial effects in encountering problems of obesity. Garlic and its extracts, when supplemented with diet, have been proven to be beneficial in animals. Garlic extracts increased the growth and metabolism of interscapular brown adipose tissue (BAT) in rats through enhanced mitochondrial uncoupling protein (UCP) content. UCP is a thermogenic protein involved in dissipating energy as heat, and garlic products increased catabolism of dietary cholesterol and fatty acids as observed in the studies on rodents.

Both black garlic and its fermented version have shown promising results in protecting high-fat diet-induced obesity, hyperglycaemia, liver and kidney damage in mice. Garlic compounds are also reported to reduce glucocorticoids, which are primarily implicated in visceral and central obesity contributing to metabolic syndrome. Furthermore, cysteine compounds of garlic decrease FAS expression, an enzyme that plays an important role in lipid synthesis, in liver cells. In mice, diet supplemented with garlic has been reported to reduce the concentration of plasma triglycerides, free fatty acids and total cholesterol. In addition, up-regulation of uncoupled proteins for fat oxidation along with a reduction of tissue mass was noticed in epididymal adipose depots, indicating the beneficial effects of garlic supplementation in improving metabolic profile and reducing adipose tissue mass.

Garlic derivatives and metabolic syndrome

Metabolic syndrome is characterized by a combination of deteriorating health conditions such as increased blood pressure, high blood sugar level, accumulation of body fat (obesity) culminating in increased risk of cardiac diseases and diabetes. Anti-oxidant properties of garlic and its compounds can help address these issues. Zinc complexes with garlic components serve as insulin-mimetic, a new therapeutic approach to treat diabetes, leptin resistance and to suppress progression of obesity in rodent models.

Garlic compounds and bone health

There is an inverse relationship that prevails between adipocytes and bone-forming osteoblasts in the bone marrow, as both adipocytes and osteoblasts are derived from a common precursor cell, the mesenchymal stem cell. Thus, there is a positive correlation between obesity and osteoporosis and incidence of osteoporosis with the progression of obesity, at least in post-menopausal women. Stimulation of adipogenesis at the expense of osteogenesis can lead to the accumulation of adipocytes in bone marrow, resulting in weaker bones. Osteoporosis and obesity have become major health concerns, as a large amount of bone mass is lost during initial years following the onset of menopause. On
the other hand, the net gain in bone formation is determined by a balance between mineralization and resorption. Several dietary constituents and herbal products including onion and garlic show promising effects on bone health by inhibiting bone resorption. The effects of garlic and its derivatives have been shown to play a positive role in reducing bone resorption in ovariectomized animal models through partial recovery of the serum oestrogen in hypogonadal rats by reducing inflammatory cytokines and oxidative stress.

Garlic derivatives counteract endocrine disruptors

Endocrine disruptors are chemicals, either natural or man-made, that interfere with endocrine system and result in some adverse health conditions such as lowered fertility, endometriosis, obesity and some types of cancer. Tributyltin (TBT) is widely considered as an endocrine-disrupting chemical and a potential obesity inducer: TBT makes its way into human beings through contaminated sea food and is implicated in oxidative damage both in vivo and in vitro research models. Pre-treatment with garlic oil has shown its ability as a scavenger in preventing TBT-induced oxidative damage by inhibiting ROS production and malondialdehyde content; in addition, it offers protection against DNA damage, nuclei and mitochondrial damage in thymocytes in mice.

Garlic compounds: toxicity

The evaluation of product toxicity is of paramount importance before a product can be considered for therapeutic use. Although garlic has been traditionally used in cooking for its flavour and aroma for several centuries without any health concerns, it is necessary to consider all toxicity issues before using it for therapeutic purposes. Some reports have even suggested using garlic derivatives in moderation, using it as a complementary rather than a therapeutic, as a result of some complications associated with its excessive consumption. Burning sensation, diarrhea and some allergic reactions have been cited as examples of side effects linked to excessive garlic consumption. However, most of these toxic effects of garlic derivatives can be eliminated by improved and sophisticated processing methods. The safety limits for each garlic compound, as tested in animal models, vary, and usually, water-soluble SAC is less toxic than oil-soluble derivatives. In addition, these differences in safety limits of garlic derivatives are a contributing factor to their biological and therapeutic potential.

Perspectives

Although several garlic-derived organosulphur compounds have shown promising results in cancer research in both in vitro and in vivo models, many of these compounds have not yet been explored for their potential to be used as therapeutics to treat obesity. There are many compounding factors that can affect the outcome of testing in different models. In animal models, absorption, gut microflora, metabolism, bioavailability and gut physiology are the key determining factors. Phytochemicals have a tendency to show more potent effects when used in combination than alone. Similar modes of increase in potency by synergism can be expected from garlic compounds when used in combinations. The key to harvesting potent products from garlic is the method of extraction and purification. One of the interesting roles of garlic is to enhance thermogenesis in BAT and some other metabolically active organs such as liver. As reported in some studies, garlic compounds have the ability to enhance the expression levels of thermogenic proteins such as UCP1. Thermogenesis induced by UCP1 is a process of non-shivering heat generation by combusting excess lipids and glucose that are accumulated in the body. Feeding some of the dietary components low in protein content can activate BAT, thereby initiating thermogenesis. As it is well known, obesity is a condition of energy imbalance with higher energy intake than expenditure. Activation of thermogenesis by BAT can be a source of increased expenditure, thereby restoring energy balance. Garlic derivatives may provide an opportunity to be explored in this direction.

Another important purpose of using garlic compounds is to inhibit adipogenesis by either reducing lipid accumulation or inducing adipocyte apoptosis. Although not all individual garlic compounds are as effective, some studies have suggested that aged garlic extracts or combining multiple garlic compounds can enhance their potential by synergism. In addition to the anti-adipogenic effect of garlic compounds, their impact on bone health is also an important area of research to explore. Garlic derivatives have the ability to lower bone resorption, which is an important phase of bone loss in osteoporosis.

Conclusion

Natural products are increasingly being considered for therapeutic purposes owing to their safety and lesser side effects compared with their pharmaceutically-formulated counterparts. Obesity and its related disorders are mostly diet-induced, and formulations based on phytonutrients such as garlic will be a better choice in treating these conditions. Improved processing technologies and combinatorial use can make garlic derivatives much more effective tools in the prevention and treatment of these disorders.

References


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