

Review Article

Role of Garlic in Chronic Diseases: Focusing on Gut Microbiota Modulation

Wei Quan Lim¹, Jia Ying Cheam¹, Jodi Woan-Fei Law¹, Vengadesh Letchumanan¹, Learn-Han Lee^{1*}, Loh Teng-Hern Tan^{1,2*}

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¹Novel Bacteria and Drug Discovery (NBDD) Research Group, Microbiome and Bioresource Research Strength (MBRS), Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, 47500, Selangor Darul Ehsan, Malaysia. wlim0012@student.monash.edu (W-QL); jche0331@student.monash.edu (J-YC); jodi.law1@monash.edu (JW-FL) vengadesh.letchumanan1@monash.edu (VL)

²Clinical School Johor Bahru, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Johor Bahru 80100, Malaysia

*Corresponding author: Learn-Han Lee, Novel Bacteria and Drug Discovery (NBDD) Research Group, Microbiome and Bioresource Research Strength (MBRS), Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, 47500, Selangor Darul Ehsan, Malaysia; lee.learn.han@monash.edu (L-HL); Loh Teng Hern Tan, Clinical School Johor Bahru, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Johor Bahru 80100, Malaysia; loh.teng.hern@monash.edu (LT-HT)

Abstract: Garlic is a herb and has been used as a spice with a long history in different types of cuisine. Garlic and its components are believed to be able to bring benefits to the health of an individual. The gut microbiota is closely related to an individual's health, and garlic is shown to have an effect on the gut microbiota as well. Hence, this literature review aims to portray the uses of garlic and its bioactive constituents on human health, particularly looking at how it modulates the gut microbiota and subsequently affects an individual's health directly or indirectly. These studies have shown the ameliorative effects of garlic and its bioactive constituents on various chronic diseases, including hypertension, diabetes mellitus, hyperlipidaemia and liver diseases.

Keywords: Garlic; allicin; alliin; gut microbiome; metabolic diseases

1. Introduction

Chronic diseases, such as hypertension, diabetes mellitus, obesity, hyperlipidaemia, and complications, including myocardial infarction and cerebrovascular accidents, are the major health concerns surrounding people all the time. It takes time, effort, and money to manage the diseases from diagnosis to treatment. They appear as some form of burden to the people, and most of the time, uncontrolled diseases will lead to complications that may

severely affect the well-being of humans. Awareness regarding the diseases has been raised, and people started taking steps to prevent the diseases and their complications. Initiatives can be made in the simplest form, including lifestyle modifications (diet modification and exercise) and taking medications.

Regarding preventative methods, garlic has been used traditionally in improving health. Garlic as a spice has not only been used to improve the taste of food, but it also has the potential to regulate an individual's health. Recently, it has been believed that garlic helps to alter the gut microbiota in good ways and further improves health. Various chronic illnesses can be prevented by supplementing garlic into our diet. Garlic and its constituent allicin, diallyl disulphide, can act as anti-inflammatory and antioxidant agents to help cope with diseases.

Gut microbiota plays a vital role in maintaining human health. The gut microbiome consists of different types of bacteria. A balanced gut microbiome system helps maintain good health by forming a good immune system and defence against pathogens^[1-7]. The components in the gut microbiota are largely affected by many factors, including inheritance, diet, and drugs^[8-11]. As inheritance is a non-modifiable factor, diet and drugs are those we can take into account and modify accordingly to help improve our health^[12-14]. The gut microbiota is in mutualism with the host, and they provide benefits to each other. The gut microbes feed on the food we consume, and on the other hand, they help to degrade and convert those complex substances to enable the gut to absorb the nutrients. Garlic has been part and parcel of our diet, and taking garlic can help to modulate the gut microbiota in a good way so that the beneficial microorganisms or the probiotics can be retained while the pathogenic species can be eliminated. Consumption of garlic in the long term will help to improve health indirectly.

This review aims to investigate recent studies to determine the benefits of taking garlic in daily life and the role of garlic and its constituents in modulating human health via gut microbiome modulation. Besides that, this review also provides an overview of how garlic prevents chronic diseases and explores the potential use of garlic as a therapeutic agent for diseases.

2. An Overview of Garlic and Its Constituents and Their Effect on Gut Microbiota

Garlic has been used widely in different cuisines. It can be consumed raw or crushed, depending on the consumers' preferences. Garlic is thought to be bringing a lot of benefits, especially towards the health of an individual. A person with a healthy gut microbiota will have a healthy immune system. Garlic and its constituents have been shown to modulate the gut microbiota composition by selectively stimulating beneficial microorganisms' growth and suppressing pathogenic species' growth. Gut microbiota is correlated to an individual's health because it affects the absorption and elimination of the food we eat. This is particularly more observed with patients with metabolic diseases as those chronic diseases are highly

dependent on diet and lifestyles^[15]. In the literature review, the aim is to investigate the effect of garlic on gut microbiota, in turn, its impact on an individual's health.

3. Composition of Garlic

Garlic (*Allium sativum* L.) is mainly comprised of water, followed by carbohydrates, protein, and organosulfur compounds. Fructans are the main component of carbohydrates, and they can provoke the growth of probiotic bacteria in the gut and subsequently improve the immune system^[1]. Organosulfur compounds (OSC) are available in most plants, but garlic's amount is higher than the other plants. The primary OSC from garlic are γ -glutamyl-S-allyl-L-cysteines (G-SAC). G-SAC is a metabolite that will later be converted to alliin and is thought to be responsible for antimicrobial activity in the gut^[1]. Alliinase will be activated during the crushing process of garlic, and it converts alliin into allicin. Allicin has a variety of actions on the gut, including antimicrobial, anticancer, antioxidant, and immune-modulating activities. Allicin will be absorbed in the intestines through the villi, and it can bypass the stomach without being affected by the low pH of the gastric acid. Allicin is then metabolised into diallyl disulphide in the bloodstream and transported to various organs. Allicin and its metabolites can be interconverted by the liver cells. This keeps allicin readily available as it can only be transported in the form of diallyl disulphide. The metabolites formed from allicin include diallyl disulphide, S-allylmercaptocysteine, S-allyl cysteine, and so on, and they are those responsible for bringing benefits to the health^[16]. Apart from that, garlic also contains a variety of minerals and vitamins, including potassium, zinc, iron, sodium, and water-soluble vitamins^[17].

4. The Effect of Garlic and Its Constituents on Gut Microbiota

Gut microbiota consists of the bacteria grown in the intestines and have a mutualistic relationship with the human host. Bacteroidetes and Firmicutes are the significant part of the gut microbiota, and other bacteria reside in the human gut^[18]. Numerous studies have investigated the relationship between garlic and its effect on gut microbiota and health^[1,19–22]. Through these studies, garlic has been shown to be able to modulate gut microbiota^[1,19,21]. One of the studies by Chen *et al.*^[23] has demonstrated that garlic supplementation in the diet increases *Lachnospiraceae* and decreases *Prevotella*^[1]. *Lachnospiraceae* is the normal flora found in the gut, and it plays a role in producing short-chain fatty acid (SCFA). SCFAs are the primary source of nutrients for colonic epithelial cells, and they exert an anti-inflammatory effect in the gut^[24]. Another study by Filocamo *et al.*^[19] suggested that using garlic powder can inhibit the growth of microorganisms in the gut. However, Lactobacilli (lactic acid bacteria) have shown resistance towards garlic powder, and these bacterial species can grow and replicate despite consuming garlic regularly. Lactobacilli are the probiotics that have an essential role in forming the barrier in the gastrointestinal system^[25]. Apart from that, they act as anti-inflammatory agents and help to prevent cancer and inflammation in the intestines^[26–30]. Studies also showed that the components present in garlic have bactericidal effects on some bacteria species, including *Escherichia coli*, *Salmonella typhimurium* and *Neisseria gonorrhoeae*^[20,31,32]. Those bacteria are the pathogen

that predisposes the host to infections^[33,34]. A study by Maeda *et al.*^[35] investigated the effect of taking aged garlic extracts on the gut microbiota profile. After seven weeks of consuming aged garlic extracts, there is an increase in the *Lactobacillus* and a decrease in several bacteria species, including *Clostridium* cluster XVIII and *Prevotella*. The use of garlic has been shown to be beneficial to the host. Garlic supplementation in the diet can expand the diversity and richness of the gut microbiome and, at the same time, help lower the pathogenic species in the gut^[36].

The ratio of Firmicutes to Bacteroidetes is closely related to obesity, and obese patients tend to have a higher Firmicutes/Bacteroidetes ratio compared to a healthy individual^[21]. The Firmicutes/Bacteroidetes ratio will increase with ageing and implementing a high-fat diet^[23]. Allicin, the main OSC present in crushed garlic, has an antibacterial effect on the gut. Consumption of garlic has been shown to reduce the ratio, and this indirectly deals with gut dysbiosis caused by a prolonged high-fat diet^[23].

A study from Zhang *et al.*^[22] demonstrates that alliin (an active component in garlic) consumption can modify the gut microbiota, especially *Allobaculum* sp. The role of *Allobaculum* spp. in the gut is to utilise glucose^[37], which helps to weight loss for obese individuals^[38]. Another study finds that alliin can induce the modulation of components in the gut microbiota. The study shows that alliin supplementation results in a decrease in the abundance of Lachnospiraceae and an increase in the abundance of Ruminococcaceae^[39]. Those are the common normal flora found in the gut, and they assist the host in degrading the complex materials from plants, such as cellulose and hemicellulose, and further aid in the absorption of the substrate to yield energy for the hosts^[40]. Those substrates cannot be digested and broken down by the host as there is no enzyme specifically targeting those substrates, and the host must rely on the gut microorganisms. Besides, the study suggested that alliin consumption helps to improve lipid and glucose profiles in the long term^[39]. This result is consistent with the increase in Ruminococcaceae as it has been proved that Ruminococcaceae has a protective function against long-term weight gain in the host^[41].

Besides alliin, fructan is also the main component found in garlic. Supplementation of garlic fructan (GF) can promote the growth of *Bifidobacterium* in the gut^[42]. *Bifidobacterium* is the beneficial normal flora in the gut, and it is linked to many health benefits, including preventing colon cancer and reducing the symptoms of inflammatory bowel disease^[43]. *Bifidobacterium* probiotic has been used to treat diarrhoea and necrotising enterocolitis in preterm neonates^[43,44]. Another study by Zhang *et al.*^[45] focuses on the effect of inulin-type fructan on the gut microbiota. After treatment with inulin, a rise in the number of short-chain fatty acid-producing bacteria and *Lactobacillus* is evidenced^[45]. Apart from that, a drop in *Desulfovibrio* is also present in the study. *Desulfovibrio* bacteria is considered a pathogen in the human host, and it is often associated with ulcerative colitis and intra-abdominal infections^[46,47]. Inulin-type fructan can affect the gut microbiota. It is noted that those receiving inulin-type fructan have softer stools, which actually improves the hosts' constipation issues^[48].

Organosulfur compounds in garlic are the hydrogen sulphide (H₂S) donors in the body^[49]. Study shows that H₂S can prevent the dysbiosis of gut microbiota caused by non-steroidal anti-inflammatory drugs (NSAIDs) and alcohol^[50]. This helps balance the system after the host is exposed to external factors like alcohol and drugs. Besides that, H₂S has been shown to prevent inflammation and foster the restoration of the damaged tissues in the gut^[50]. Propyl-propane thiosulfonate (PTSO) from garlic also exerts anti-inflammatory effects and helps restore the epithelial tissues' barrier function in the intestines^[51]. This suggests that garlic may help with inflammatory bowel diseases in the future.

5. The Effect of Garlic on Chronic Diseases

Many studies have shown that garlic can directly or indirectly improve the health of an individual, which may link to the modulation of gut microbiota (Figure 1). Supplementation of garlic in diet can affect health in a good way. The human gut microbiota helps to degrade complex substances, produce short-chain fatty acids, and maintain homeostasis in the intestines. When there is microbial dysbiosis, problems start in the host, such as metabolic syndromes, allergies, and neurological and gastrointestinal diseases^[52–55].

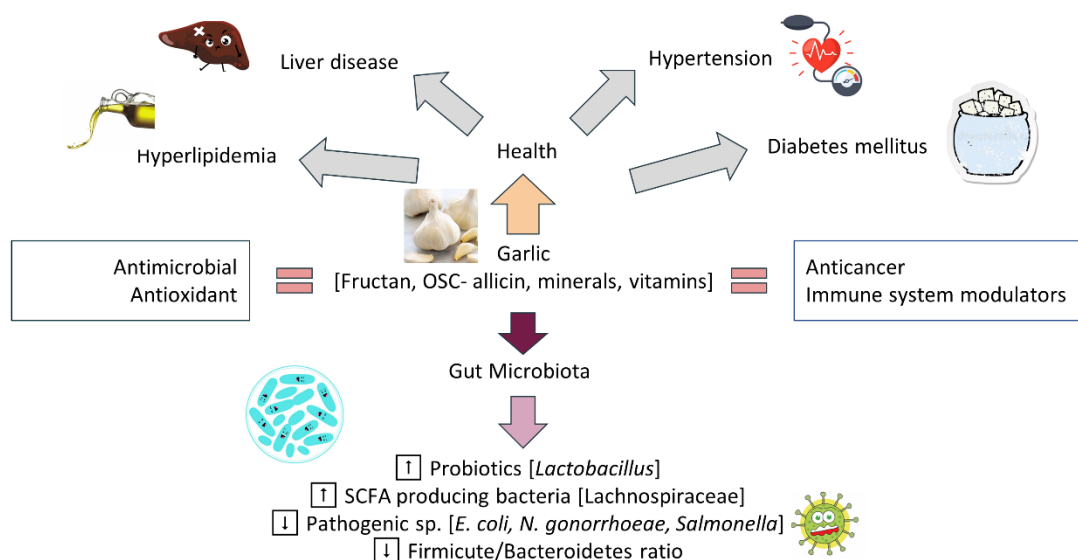


Figure 1. Summary of garlic's gut microbiome modulation effect in improving overall health and metabolic syndromes.

5.1 Hyperlipidaemia

Practising a diet high in fat content in the long term affects gut microbiota composition. The high-fat diet increases the number of pathogenic bacteria such as Proteobacteria, *Desulfovibrio*, and Actinobacteria in the gut. These pathogenic bacteria tend to be pro-inflammatory and affect energy uptake, leading to obesity^[56]. In previous studies, garlic has been shown beneficial in lowering cholesterol levels and ameliorating the lipid profile. One shows that consuming garlic can improve dyslipidaemia caused by a high-fat diet^[23]. Another study found that intake of aged garlic extract may help decrease fat uptake

from the intestines and thus suppressing the deposition of triglycerides in the liver^[35]. Black garlic melanoidins (MLD) can target obesity issues as they effectively slow down the weight gain process caused by the high-fat diet. Besides, MLD can also inhibit lipid accumulation in the liver and assist the lipid metabolism process, improving the lipid profile among patients with dyslipidaemia^[57]. A high-fat diet usually leads to a change in the gut microbiota, and a study reveals that implementing low molecular and high molecular melanoidins can reverse the changes and eventually relieve the disrupted rhythm of gut microorganisms^[58]. Allicin from garlic helps the browning of white adipose tissue and further prevents the gaining of weight caused by a high-fat diet^[59]. Allicin can stimulate lipolysis in the body as well as contribute to thermogenesis, and these are ways to burn fat and relieve obesity issues^[59]. Inulin, as a substrate found in garlic, is also able to promote weight loss in patients with obesity. After 3 months of an inulin-rich diet, the participants experienced a drop in their BMI and had better blood pressure and sugar profile^[60].

5.2 Liver diseases

A high-fat diet causes metabolic syndrome such as obesity, eventually leading to liver diseases. Dysbiosis of gut microbiota can lead to liver inflammation and fibrosis. This occurs through the change in the yielding of energy from the diet, an increase in intestinal permeability that leads to the presence of bacterial products in the bloodstream, the formation of ethanol and changes in the metabolism of choline, bile acid, and lipid^[61]. Choline deficiency predisposes an individual to non-alcoholic fatty liver disease by increasing lipid deposition in the liver^[62]. Not only does garlic target dyslipidaemia, but garlic also helps with liver inflammation. Garlic supplementation in the diet can relieve inflammation in the liver by reducing alanine transaminase (ALT) and aspartate transaminase (AST) and normalising the lipid profile. This suggests that garlic may potentially treat alcoholic liver fibrosis^[63]. Diallyl disulphide was used to address the issue of liver inflammation, and it was found that diallyl disulphide can suppress inflammation, lipid metabolism, and peroxidation^[64]. Non-alcoholic steatohepatitis (NASH) can be targeted using garlic as a therapeutic agent. Another study has used garlic essential oil and diallyl disulphide, and the result shows that they can prevent non-alcoholic fatty liver disease (NAFLD) by suppressing inflammation and lipid accumulation^[65]. A study from Shunming *et al.*^[66] revealed that high amounts of raw garlic could help lower the prevalence of NAFLD among men but not women. This can be due to allicin's bioactivity, which exhibits anti-inflammatory and antioxidant effects that stop the progression of NAFLD^[66]. On the other hand, a study by Yang *et al.*^[67] shows that diallyl disulphide (DADS) can modulate the gut microbiota by lowering the number of Bacteroides and raising the number of Firmicutes. These have been seen in patients with obesity and those on a high-fat diet. DADS alters the expression of genes responsible for lipid metabolism, and a low dose of DADS, along with a high-fat diet, increases fat deposition in the liver^[67]. The results from this study are different from the other studies where garlic has consistently shown to have the ability to target obesity and liver diseases. More studies need to be done to explore garlic's effect on patients' lipid profiles.

5.3 Hypertension

Gut microbiota plays a vital role in regulating blood pressure as well. They modulate the uses of the energy, metabolism of catecholamines in the gut, and transportation of ions through the gastrointestinal system^[68]. Production of short-chain fatty acids switches on receptors such as G-protein coupled receptors and olfactory receptors, which work to balance blood pressure^[68]. A rise in Firmicutes to Bacteroidetes ratio puts an individual at a higher risk of developing hypertension, and garlic can help to lower the ratio. On the other hand, Lactobacilli helps to inhibit angiotensin-converting enzymes and subsequently lowers blood pressure^[68]. This works similarly to the drugs ACE inhibitors used for hypertensive patients. Garlic can lower blood pressure among hypertensive patients. Kyolic aged garlic supplementation prevents the stiffening of arteries caused by ageing via lessening the pulse wave velocity and thinning the blood to lower the risk of thrombosis^[69]. This overall improves the cardiovascular health of an individual.

Allicin found in garlic is able to inhibit the formation of trimethylamine-N-oxide (TMAO)^[70]. The gut microbiota forms TMAO through the metabolism of carnitine, and it acts to promote atherosclerosis^[70]. Hence, we can deduce that consumption of garlic in the long term will decrease the risk of atherosclerosis.

Furthermore, garlic-derived organic polysulfides have been shown to exhibit vasoactivity. A study showed that several garlic-derived organic polysulfides acted as an H₂S donors and boosted endogenous H₂S production in blood and tissues. H₂S can promote vasorelaxation of the vessels and indirectly help promote the health of the cardiovascular system^[71]. A more recent animal study by Hsu *et al.*^[72] revealed that garlic oil supplementation protected adult male offspring from hypertension induced by a perinatal high-fat diet given to the mother during pregnancy and lactation. Interestingly, garlic oil was shown to mediate the hypertension preventive effect with modulations of gut microbiota composition, microbiota-derived metabolite SCFAs, H₂S-generating pathway, and NO bioavailability. Genus *Lactobacillus* was found to be increased in abundance, while *Tunricibacter* and *Staphylococcus* were decreased in the garlic oil supplementation group^[72].

5.4 Diabetes mellitus

Patients with diabetes mellitus tend to show some changes in the gut microbiota to some extent. There is an increase in the pathogens and a decrease in the butyrate-producing bacteria in the intestines^[73]. Diabetic patients have a higher number of *Lactobacillus* species in the gut, and those species have a positive correlation with fasting glucose and HbA1c levels^[74]. Garlic has a beneficial effect on the blood glucose profile of diabetic patients as well. Aged garlic extract used in the study has been demonstrated to improve insulin insensitivity^[35]. Another study focused on the effect of alliin and found that the use of alliin increased the sensitivity to insulin and augmented glucose homeostasis in the body^[39]. This will prevent fluctuation of glucose levels after meals and help diabetic patients better control

their serum glucose levels. A study by Zhang *et al.*^[75] also found that allicin from garlic maintained glucose homeostasis, suggesting that it could be used to treat metabolic disorders.

6. Conclusion

Consumption of garlic has been demonstrated in many studies that it can modulate the gut microbiota by enhancing probiotics' growth and suppressing pathogenic microorganisms' growth. Studies showed that garlic has the potential to become a complementary alternative medicine to a lot of diseases. Thus, garlic is a great functional food containing bioactive constituents with immense potential to be developed as an anti-inflammatory, lipid-lowering, glucose-lowering, and antihypertensive agent.

Numerous studies have been conducted, and garlic has been portrayed as a beneficial agent for health conditions. It can modulate gene expression in the gut and the gut microbiota. Apart from that, garlic can be used to improve blood pressure, blood glucose profile, and lipid profile, and most importantly, garlic is a natural organic substance. It can effectively reduce the number of medications needed by a patient by substituting them with natural substances. However, most studies were done on the animal model. Future studies should be conducted on a large scale in humans to understand better the underlying mechanisms of garlic in conferring better health outcomes.

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