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Ginger Extract and Ginger Nanoparticles; Characterization and Applications

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ABSTRACT

Herbal plants have been used by a majority of people due to its pharmacological properties. Recently, herbal medicinal is got more attention by scientist due to appearance of antibiotic resistant bacteria. Ginger is a one of medicinal plant which used around the world as flavoring agent in food in both fresh and dried forms. Also, ginger has multiple therapeutic action such as anti-tumorigenic, anti-apoptotic, anti-oxidant activities which attributed to its active polyphenol compounds as gingerols and shogaols. Recently, ginger nanoparticles have been isolated from ginger extract and involved in drug delivery system without induction of side effects. This review paper briefly summarizes the pharmacological characterization and different therapeutic applications of ginger in both extract and nano-size form.

Key words: Ginger, ginger nanoparticles, gingerols, shogaols, herbal medicine.

INTRODUCTION

Most of people around the world depending on herbal medicine to solve their health problems (Bekele and Reddy, 2015). Recently, herbal plants which have medical importance are got more attention by scientist due to appearance of antibiotic resistant bacteria (Sibanda and Okoh, 2008). Ginger (*Zingiber officinale*) is one of most common herbal plants which belong to the Family Zingiberaceae (Mekuriya and Mekibib, 2018). Roots of ginger are characterized by pale yellowish, aromatic, thick leaves and reach about 2 m in height (Jyotsna *et al.*, 2017). Ginger was cultivated in South-East Asia in humid regions (Semwal et al., 2015). Also, extract of ginger was reported to have essential oils, phenolic compounds, flavonoids, carbohydrates, proteins, saponins, and steroids, terpenoids (Jyotsna *et al.*, 2017). Several studies showed that, ginger has multiple pharmacological activities like anti-oxidant, anti-inflammatory, anti-apoptotic actions which attributed to its phenolic compounds such as gingerols and shogaols which consider the most important an active ingredients present in ginger root (Poorrostami *et al.*, 2014). So, ginger has been included in treatment of various diseases such as fever, pain, inflammation (Yang *et al.*, 2014), diabetes (Al-Amin *et al.*, 2017), obesity (Akinyemi *et al.*, 2016), diarrhea (Ahmad *et al.*, 2015), rheumatoid arthritis (Rashidian *et al.*, 2014), many types of cancer (Romero *et al.*, 2018) and Alzheimer disease (Karam *et al.*, 2014).

Active ingredients of ginger

The active components which present in ginger have been divided into volatile and nonvolatile compounds such as gingerols, shogaols, paradols, and zingerone (Ahmed *et al.*, 2015). pharmacological effects of ginger are attributed to phenolic compounds such as gingerols and shogaols which consider the most important an active ingredients present in ginger root (Poorrostami *et al.*, 2014 ; Hasan *et al.*, 2016). Gingerol and shogaols are composed of 6-, 8- and 10- structural analogs (Mekuriya and Mekibib, 2018). Biologically all gingerol analogs act identically in the body , but they are different in quantities and potency (Chan *et al.*, 2011) The differences in their structure can be seen below in Fig. 1. Shogaols are dehydrated form of gingerols, and so their structures are similar but different in mechanism of action (Semwal *et al* ., 2015). Shogaols has stronger antioxidant and biological effects than gingerols due to it was absorbed faster and the t1/2 was longer than gingerols (Li *et al.*, 2019). A comparison of the structure of 6-gingerol and 6-shogaol is shown below in Fig. 2 and contents of the bio-active compounds found in 1g of dried ginger are shown in Table 1.

Stability and distribution of ginger component in the body

The stability and distribution of the ginger components including (6-gingerol, 6-shogaol, 8-gingerol, 8-shogaol, 10-gingerol, 10-shogaol, Zingerone and 6-isodehydrogingenone)

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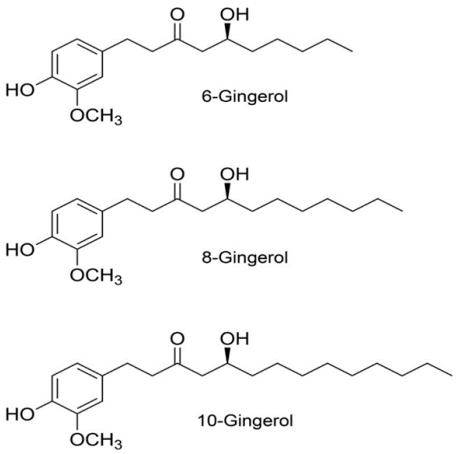

Fig. 1: The structure of 6-gingerol, 8-gingerol and 10-gingerol (Chan *et al*., 2011).

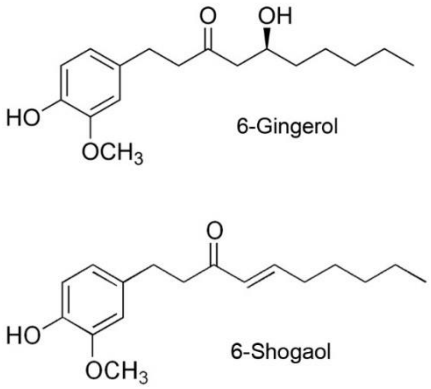

Fig. 2: The structure of 6-gingerol and 6- shogaol (Chairat and Sirichote, 2008).

Table 1: The typical contents of the bio-active compounds found in 1g of dried ginger (Schwertner *et al*., 2006).

Compound	Amount
6-Gingerol	17-19mg/g
8-Gingerol	0.47mg/g
10-Gingerol	0.36mg/g
6-Shogaol	1.27mg/g
8-Shogaol	0.0012mg/g
10-Shogaol	N/A

were assessed in plasma and different organs of rats after administration of ginger extract orally at dose of 400 mg/kg. The results showed that, ginger components were stable under different condition such as (4°C) for one day and (–20°C) for one month (Li *et al.*, 2019).

After oral administration, ginger ingredients were distributed in different organs such including stomach, intestine, liver, lung and kidney which considered as target organs. The components reach to maximum concentration rapidly and decreased after 3 hours, and the component were metabolized and eliminated mainly by liver and kidney respectively. Also 6-shogaol and Zingerone can distribute through blood brain barrier and reach to the brain (Li *et al.*, 2019).

Molecular targeting and anti-cancer effect of ginger

Ginger component could modulate the expression of several genes including several proteins, transcription factors, enzymes such as antioxidant enzymes including MDA, GSH, SOD, CoA and glutathione peroxidase and inflammatory mediators such as cytokine TNF-α (Jeena *et al.*, 2013). So, ginger and its active ingredients could be included in several cancer models such as:

Gastrointestinal tract cancer: 6-gingerol and 6-shogaol have anticancer activities against cancer of gastrointestinal tract by targeting several cellular molecules such as NF-κB, TNF-α, Bcl-2, caspases, and other cell growth regulatory proteins that play an important role in tumorigenesis, cell survival, cell proliferation, invasion, and angiogenesis (Prasad and Tyagi, 2015).

Pancreatic cancer: 6-gingerol has the ability to arrest the cell cycle of pancreatic cancer at G1 phase and blocking the S phase entry by decrease the production of cyclin A and cyclindependent kinase (Cdk) expression (Park *et al.*, 2006). Also 6-gingerol suppress the expression of extracellular signal-regulated kinases (ERK) pathway which lead to inhibition of invasion and metastasis of pancreatic cancer cells (Islam, 2014).

Liver cancer: Ginger has been reported to increase the levels of antioxidant enzymes, improvement of hepatic markers and reduction in acute inflammation which induced by multiple toxicities (Jeena *et al.*, 2013; Gholampour *et al*., 2017). Also, Prasad and Tyagi (2015) have shown that, 6-shogaol has important role in prevention of Mahlavu hepatoma by inducing induce apoptotic cell death of cells via an oxidative stress-mediated caspase-dependent mechanism.

Breast and ovarian cancer: Ginger extract was reported to protect female Wistar rats against breast cancer which exposed to 7, 12-dimethyl-benz[a]anthracene at a dose of 20 mg/kg orally for 4 months to induce cancer. Ginger extract upgraded the histological structure of breast tissues and improved the serum levels of anti-oxidant enzymes, in addition to downregulated of multiple genes such as GST-P, CYP1A1, CYP1B1, and vascular endothelial growth factor-receptor 1 and Bax which associated with tumor incidences (Soliman and Elfeky, 2016). Also, ginger reported to has inhibitory effect against ovarian cell line (Pashaei-Asl *et al.*, 2017).

Skin cancer: 6- gingerol has the ability to inhibit skin cancer in mouse skin model by arrest initiation and promotion stages (Chung *et al.*, 2001). Another study showed that, 6-gingerol has inhibitory effect on both 12-O-tetradecanoylphorbol-13-acetate (TPA) (Jyotsna *et al.*, 2017), and COX-2 expression which induced skin cancer (Kim *et al.*, 2005).

Anti-oxidant activity of ginger

The protective action of ginger against multiple toxicities is attributed to its anti-oxidant action. Ginger extract could increase the gene expression of anti-oxidant enzymes such as GSH, SOD and MDA (Jeena *et al.*, 2013). Ginger consumption was effectively inhibit the levels of both superoxide production and catalase (Ahmed *et al.*, 2008), suppresses lipid peroxidation and modified the levels of reduced glutathione (El-Sharaky *et al.*, 2009), and effectively reduce inducible nitric oxide synthase (iNOS)

expression which is increased in multiple stress (Koh *et al.*, 2009) and produce nitric oxide which lead to DNA damage (Ippoushi *et al.*, 2003). So, ginger could be used as strong antioxidant in both *in vivo* and *in vitro* and reported to reduce age-related oxidative stress marker (Topic *et al.*, 2002).

Several studies showed that, ginger could protect liver against several toxicities due to its anti-oxidant effect and scavenger of free radical. The hepatoprotective effect of ginger against carbon tetrachloride was investigated by Hasan *et al.* (2016), who find that, ginger decreased the level of lipid peroxidation and increased glutathione enzyme**.** Also, ginger could protect the liver against carbofuran (pesticide) (Ahmed *et al.*, 2015), metalaxyl (fungicide) (EI-Ghonaimy, 2015), lead toxicity (Mannem, 2014), cisplatin (Attyah and Ismail, 2012), mancozeb (fungicide) (Sakr, 2007), lamotrigine (antiepileptic drug) (Poorrostami *et al.*, 2014), and paracetamol toxicity (Ajith *et al.*, 2007) through improving the liver function markers such as (ALT and AST) and normalized the levels of multiple oxidative stress markers in addition to upgrading the histological structure of liver cells.

Ginger extract was reported to protect the kidney against oxidative stress which induced by alcohol and improve the kidney marker suck as urea and plasma creatinine, in addition to adjustment the profiles of plasma electrolyte (Maralla, 2013). Also, [6]-gingerol and [6]-shogaol could enhance the kidney function in rat suffering from oxidative stress and renal toxicity which induced by cadmium (Gabr *et al.*, 2017). In addition to protect kidney against ferrous sulfate-induced hepatic and renal toxicity by reducing lipid peroxidation and chelating iron (Gholampour *et al.*, 2017).

Ginger has been used as protective agent against ultra violet B which cause inflammatory skin disorders by producing of multiple free radicals (Kim *et al.*, 2007), ginger also used as reduced the hazard of exposure to gamma radiation in mice through decrease the production of lipid peroxidation (Jagetia *et al.*, 2003).

Anti-inflammatory effect of ginger

Ginger extract has been used as anti-inflammatory element due to its ability to decrease inflammation, swelling, and pain (Minghetti *et al.*, 2007). So, it could be involved in treatment of stomach ulcer (Badreldin *et al.*, 2008), and colitis which induced by intracolonic instillation of 2 mL of 4% (v/v) acetic acid in Wistar rat for five days. Ginger volatile oil in multiple doses (100, 200, and 400 mg/kg/orally) could decrease colon weight/length ratio and the high doses (200 and 400 mg/kg) decrease the severity of ulcer while the dose of 400mg/kg decrease the severity of histopathological lesion in colon (Rashidian *et al.*, 2014). Also, ginger reported to be effective against osteoarthritis and rheumatism (Reginster *et al.*, 2000).

Several studies showed that ginger may exhibit anti-inflammatory effects through increase heat production that associated with vasoconstriction of adrenergic receptors (Bode and Dong, 2011). The anti- inflammatory effect of ginger may be attributed to gingerols which known to be TRPV1 (transient receptor potential vanilloid subtype 1) agonists, which is a heat-and pain-sensitive receptor (Dedov *et al.*, 2002) by enhancing the intracellular calcium concentration (Iwasaki *et al.*, 2006), in addition to suppress the production of proinflammatory cytokines such as tumor necrosis factor α (TNF-α),interleukin (IL)-1β, and IL-12, from macrophages (Tripathi *et al.*, 2008). On the other hand, 8- gingerol had ability to inhibit cyclooxygenase-2 (COX-2) expression, which increased the formation of prostaglandins and induction of inflammation (Tjendraputra *et al.*, 2001).

Neuro-protective activity of ginger

The mechanism of neuroprotective action of ginger is not fully known but it may be attributed to the anti-oxidant effect of active bio-ingredient. 6- shogaols could inhibit the microglia cells during the occurrence of transient ischemia (Jyotsna *et al.*, 2017). Another study was done by Zeng *et al.* (2013), who reported that, ginger induced an improvement in Alzheimer- induced rat. In addition to reduction in brain Ach and increase AchE levels with upgrading of histopathological finding of brain tissues.

Effect of ginger on cardiovascular and blood clotting

Administration of a low dose of ginger orally or IP did not change the serum level of platelet thromboxane-B2 (TBX2), while the same dose orally leads to decrease of prostaglandin-E2 (PGE2) production. The high dose of ginger (500 mg/kg) induced decrease in the serum level of PGE2 when given either orally or IP. While, the reduction in TXB2 level occurred only when administrated orally (Thomson *et al.*, 2002).

Several studies have been showed that ginger has been involved in treatment of multiple cardiovascular diseases due to its anti-inflammatory, antioxidant, antiplatelet, hypotensive, and hypolipidemic properties Wang *et al.*, 2017). Administration of ginger extract in mice induced normalization of serum levels of plasma triglycerides and cholesterol, low-density lipoprotein (LDL)-associated lipid peroxides, and LDL aggregation in addition to upgrading of histological lesions (Bianca *et al.*, 2000). On the other hand, ginger was reported to has no effect on blood pressure, heart rate and does not interact with anticoagulant drugs as warfarin (Weidner and Sigwart, 2000).

Anti-diabetic and hypolipidemic properties of ginger

Ginger administration significantly decreased the level of serum C-reactive protein (CRP) and normalized glycaemia index and lipid profile (Tabibi *et al*., 2016)**.** On the other hand, another study showed that ginger had no effect on serum CRP in lower doses that the reason of administration of a higher dose of ginger in the other studies (Imani *et al.*, 2015). Additionally, raw ginger decreased the level of proteinuria in the diabetic rats. Thus, ginger may be of great value in managing the effects of diabetic complications in human subjects lowering serum glucose, cholesterol and triacylglycerol levels in the ginger-treated diabetic rats compared with the control diabetic rats (Al-Amin *et al.*, 2017).

Veterinary importance of ginger

Cattle: Ginger has the ability to increase feed up take by improving the nutrients palatability due to its spicy taste. Also, ginger improve the formation and excretion of bile acids which lead to enhancement of digestion, absorption of nutrients and inhibition the growth of harmful bacteria in intestine (Shams Al-dain and Jarjeis, 2015).

Equine: Ginger decrease the period of recovery in racing horses without any effect on different physiological parameters such as heart rate, blood pressure and body or rectal temperature (Mekuriya and Mekibib, 2018).

Poultry: In broilers and layers, ginger powder lead to increase the body weight, growth rate and increase the production of eggs when used in variable doses for different periods (Khan *et al.,* 2012). Also, ginger reported to has antibacterial action against *Mycoplasma gallisepticum* which cause chronic respiratory disease in chicken (Sutardi *et al.,* 2015).

Fish: ginger used in aquaculture to improve the general immune state against infection disease caused by several micro-organism such as *E. coli* and *Staphylococcus aureus* (a common cause of skin infections) in addition to fungi, including *Candida albicans* (Shakya, 2015). Also, ginger has strong anti-oxidant effect and may improve the health state of fish against antibiotic resistant bacteria (Mekuriya and Mekibib, 2018).

Limitations of ginger

Ginger is one of worldwide herbal plant which used in several medical purpose without causing side effects (Poorrostami *et al.,* 2014). The ginger preparation was administrated to pregnant female rats during the second week of gestation. Rat were killed and examined at 21 day. There were not any signs of mortality and no teratogenic effects in fetus (Weidner and Sigwart, 2001). On the contrary, ginger have been reported to induce advanced skeletal development in fetus without gross morphologic malformations or fetus death (Wilkinson, 2000)**.** However, ginger is effectively an emetic drug during pregnancy (Marcus and Snodgrass, 2005). Some other minor side effects associated with ginger such as diarrhea in human when received ginger orally dose of 400 mg of ginger (3 times per day for two weeks), Ginger may cause heartburn, and in doses higher than 6 g may act as a gastric irritant. Inhalation of dust from ginger may produce IGE-mediated allergy (Chrubasik *et al.,* 2005).

Ginger nanoparticles (GNPs)

Multiple natural nanoparticles present in our diet are absorbed through gastrointestinal tract and pass to the liver and various organs. So, natural nanoparticles can provide safe method to deliver the therapeutic agent to multiple organs without induce side effects and improved drug bioavailability within the target cells (Khalil *et al.,* 2016). The nanoparticles which isolated from edible plants characterized by more easily isolation for high amount production compares with synthetic nanoparticles (Zhang *et al.,* 2016b).

Recently, ginger nanoparticles (GNPs) have been isolated from ginger roots by using super high-speed centrifugation. GNPs were identified by using ultrasonic dispersion which showed that, GNPs were 230 nm in diameter and had a negative electrical potential. Also, GNPs have specific natural membrane lipids with a few membranes proteins and contain miRNAs and different concentrations of 6-gingerol and 6-shogaol (Zhuang *et al.,* 2015).

The lipids of GNPs are consisting of phosphatidic acid (25–40%), digalactosyldiacyl-glycerol (25–40%), mono-galactosyldiacyl-glycerol (20-30%) and other lipids, such as phosphatidylglycerol, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol and phosphatidylserine. The protein of GNPs is comprised of cytosolic proteins, such as actin and proteolytic enzymes, in addition to a few membrane proteins, such as membrane channels/transporters. Also, GNPs contain high amount of microRNAs (15–27 nucleotides in length) which playing a critical role in molecular targeting and regulating gene expression. (Zhang *et al.,* 2016).

Stability of GNPs in stomach

The stability of ginger nanoparticles in stomach was evaluated *in vivo* by evaluating the Zeta potential and size of nanoparticle in stomach- or intestine-like solution and phosphate-buffered saline (PBS). The size of nanoparticles was decreased in both stomach- or intestine-like solutions compared with PBS. One the other hand, Zeta potential was negatively charged in PBS and intestine like solution due to neutral pH value, while in stomach like solution, Zeta potential was positively charged which attributed to acidity of its PH value (Zhang *et al.*, 2017).

An *in vivo* distribution of orally administered ginger

After oral administration of DiR fluorescent labelled GNPs, the signals were detected after 12 hours in liver which confirmed by estimation of albumin level using immune- staining. So, liver was considered to be the primary organ targeted by GNPs after oral administration. Ginger nanoparticles also detected in the mesenteric lymph nodes, however no any nanoparticles were detected in the spleen, lung and other organs. The efficiency of uptake of GNPs was depended on temperature. Uptake rates were very slow at 48C and increased by raising the degree of temperature , so metabolic energy is required for GNPs uptake (Zhuang *et al.,* 2015).

The effects of GNPs on body weight, hematological parameters and histological analysis

Ginger nanoparticles did not induce any changes in blood parameters as well as serum levels of proinflammatory cytokines significantly such as interleukin (IL)-6, IL-1β or tumor necrosis factor (TNF-α) after intravenous injection. Also, the histopathological evaluation of different organs reveled no changed in tissues structure such as infiltration of inflammatory cells, necrosis or vacuolation (Zhang *et al.,* 2016a).

In another study, group of mice was treated orally with GNPs for one week. The result showed that nanoparticles of ginger did not cause any changes neither in the body weight or in blood parameters compared with control group. In addition to, histological structure of different organs such as GIT, liver, kidney, spleen and lung appeared normal without any noticed changes. Thus, the data suggest that GNPs did not induce any signs of toxicity and provide safe method for drug delivery (Zhang *et al.,* 2018).

Apoptotic Activity of ginger nanoparticles

Ginger nanoparticles have been reported to induce apoptotic activity against chemical-induced cancer such as Tetracholorodibenzo-p-dioxin (TCDD) which induced colon cancer in male rats**.** Rats were treated with TCDD for one month orally using variables doses (0.2, 1, 5 and 20

µg kg), after that GNPs were induced to the rat at the initiation stage of carcinogenesis for two months at dose of (50 mg kg/daily). The results showed that, GNPs induced down-regulation of multiple apoptotic gene expression such as Bcl-2, Bax and p53 while up-regulation of apoptotic gene expression were recorded in TCDD treated rats. Moreover, GNPs enhanced the levels of antioxidant enzymes and decreased necrotic/apoptotic rate compared with TCDD treated group (Abdu *et al.,* 2017).

GNPs for colitis and colon drug delivery

Oral administration of GNPs did not induce any side effects, but it could help in treatment of colitis. Moreover, GNPs characterized by stability during transition through gastrointestinal tract and once reached to colon, they were up taken by macrophages even in presence of inflammation. So, GNPs could be used in delivery of drug to colon (Zhang *et al.,* 2017). These results were in the same line of previous studies which revealed that grape seeds are characterized by stability inside intestinal lumen and target the colon (Wang *et al.,* 2016), but GDNPs are more effective when compared with the action of nanoparticles from grape and grapefruit nanoparticles which primarily targeted intestinal stem cells (Zhang *et al.,* 2016a).

Another study showed that GNPs could be included in delivery of doxorubicin drug to targeted colon cancer cells, moreover; it enhanced the inhibition the growth of tumor compared with free drug administration and decreased the side effects of Dox such as leucopenia, thrombocytopenia, anemia and gastrointestinal disturbance. The stability of GNPs-Dox complex may be attributed to the difference of Zeta potential of the surface. Dox has a positive charge, and most of ginger particles have negative charge. On the other hand, the releasing of loaded drug was increased in acidic PH which increased the efficacy of the drug inside the intestine (Zhang *et al.*, 2016a).

Ginger nanoparticles protection against alcohol induced liver damage

Alcohols are metabolized in liver and could cause liver injury through induction of apoptosis, degenerative change and fibrosis of hepatocytes in addition to production of ROS and pro-inflammatory cytokines. Administration of GNPs orally could protect the liver against the toxic action of alcohol. The protectivity of GNPs against alcohols attributed to shogaols, which an important active component of ginger. Shogaols in GNPs are able to control several biological processes in liver including metabolism of drug and antioxidant defense mechanism. Shogaols which present in ginger nanoparticles are found in bind form, so less amount of shogaols are needed to give the same effect when compared with shogaols in ginger powder which present in free form (Zhuang *et al.,* 2015).

Protective effects of ginger nanoparticles against hepatotoxicity and nephrotoxicity relative to ginger extract

Judgement of the protective activity of ginger nanoparticles relative to ginger extract at dose of 120 mg/kg against acetaminophen toxicity at dose of 375 mg/ kg (1/10 LD_{50}) daily for three months in male rats from the histological and biochemical aspects. Serum Alanine aminotransferase and aspartate aminotransferase were determined. In addition, urea and uric acid levels were evaluated in serum. Moreover, oxidative stress was evaluated by determining malondialdehyde content and catalase enzyme activity. Meanwhile, histopathological changes in liver and kidney tissues were observed. The present study indicates that liver and kidney biochemical markers, oxidative stress and histopathological structure are improved in rat pretreated with ginger extract. However, rats treated with GNPs were more protective relative to ginger extract pre-treated rat (Bakr *et al.,* 2019).

Antimicrobial activity of ginger nanoparticle

Ginger nanoparticles could inhibit the growth of variable bacteria such as *Escherichia coli, Pseudomonas aeruginosa*, *Salmonella typhimurium, Streptococcus pyogenes, Staphylococcus aureus, Bacillus subtilis, Rhizopus sp, Aspergillus nige*, *Candida albicans*. The bacterial growth was evaluated by using disc diffusion assay. On the other hand, GNPs not induce any inhibition in the growth of yeast and mold So, GNPs could be used as antibacterial agent in food and drug industry (Norhidayah *et al.,* 2015).

Conclusions

Clinical studies from latest years have been reported that ginger has pharmacological effects such as anti-inflammatory, cardiovascular activities, anti-cancer activities, and antioxidant activity which attributed to gingerols and shogaols which exhibit a strong anti-oxidant and anti-apoptotic actions. Transforming the natural particles of ginger to nanoparticles (nanosizing) is supposed to give good therapeutic results compared to the extract form of ginger. It may be attributed to the small size of nanoparticles which makes them proper for therapeutic effects. Moreover, the ingredients of ginger nanoparticles could be widely distributed in various organ and being stable for long time by gathering themselves within the cells and remain in colloidal state without coagulating for many hours. So, GNPs supposed to provide a safe method for drug delivery without inducing side effects.

Authors contribution

AFB collected all the paper which needed to write the review and drafted the manuscript. SSA, OSE and AMB interpreted the review and made the final revision.

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