

Review Article

Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities

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Abstract: The current mode of treatment based on synthetic drugs is expensive and also causes genetic and metabolic alterations. However, safe and sound mode of treatment is needed to control the diseases development and progression. In this regards, medicinal plant and its constituents play an important role in diseases management via modulation of biological activities. Ginger, the rhizome of the *Zingiber officinale*, has shown therapeutic role in the health management since ancient time and considered as potential chemopreventive agent. Numerous studies based on clinical trials and animal model has shown that ginger and its constituents shows significant role in the prevention of diseases via modulation of genetic and metabolic activities. In this review, we focused on the therapeutics effects of ginger and its constituents in the diseases management, and its impact on genetic and metabolic activities.

Keywords: Ginger, anti-tumour activity, anti-microbial activity, neuro-protector effect

Introduction

Although, allopath based treatment is effective in diseases cure but also alters the various metabolic and molecular pathways. Since ancient time, medicinal plants and its constituents have been used for diseases management. Medicinal plants and its constituents such *curcumin*, black seed, olive fruits/leaves and dates shows a therapeutic role in diseases control via modulation of biological activities [1-3]. In Islam, herbs and its constituents have important value in diet and treatment of various diseases and Prophet Mohammed (PBUH) used various herbs including dates and *Nigella sativa* and also recommended various medicinal plants in the diseases cure [4]. Medicinal plants and their constituents show a vital effect in the diseases cure especially with properties of being antioxidant, anti-inflammatory, anti-diabetic and anti-tumour effect. Ginger, the rhizome of the *Zingiber officinale* is commonly consumed dietary condiments [5], generally

considered to be safe [6] and used to cure various diseases (**Figure 1**). It also shows a role in cancer prevention by inactivating and activating various molecular pathways. In this review, we summarized the therapeutics role of ginger in diseases management via modulation of biological activities including anti-inflammatory and anti-oxidative activities together with regulation of genes mechanism of action.

Chemical structure of active constituents

Numerous active ingredients are present in ginger including terpenes and oleoresin which called ginger oil. Ginger also constitutes volatile oils approximately 1% to 3% and non-volatile pungent components oleoresin [7]. The major identified components from terpene are sesquiterpene hydrocarbons and phenolic compounds which are gingerol and shogaol [8] and lipophilic rhizome extracts, yielded potentially active gingerols, which can be converted to shogaols, zingerone, and paradol [9] (**Figure 2**).

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Figure 1. Ginger plant and roots.

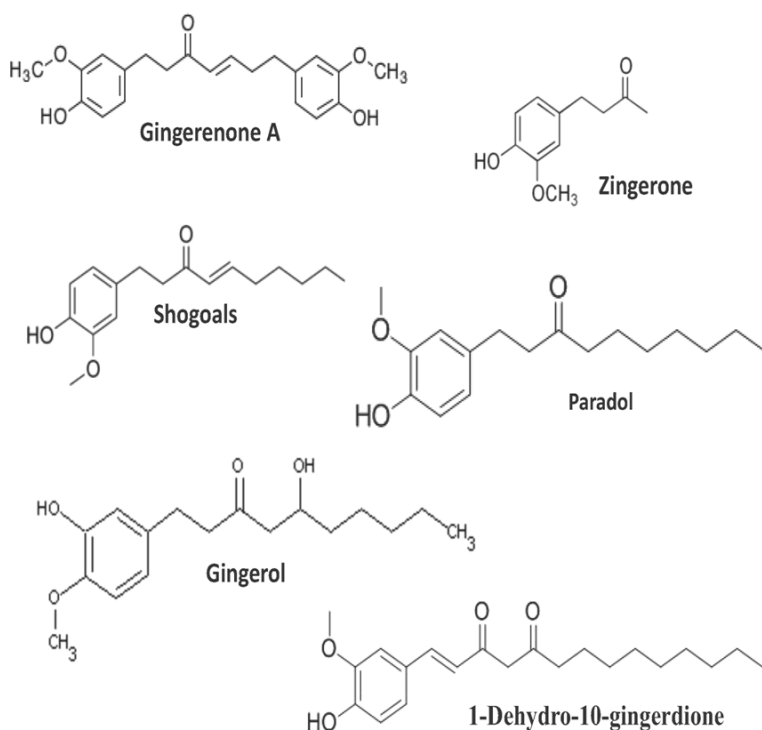


Figure 2. Chemical of structure of active ingredients of Ginger.

Mechanism of action of ginger in diseases management

Ginger, the rhizome of the *Zingiber officinale*, plays an important role in prevention of diseases (Table 1). But the exact mechanism of action in diseases management is not understood fully. It is thought that ginger act as anticancer due to various constituents such as vallinoids, viz. [6]-gingerol and [6]-paradol, shogaols, zingerone, and galanals A and B [10-12] and constituents show a therapeutics role in diseases control via modulation of various biological

activities as describe as following:

1. Ginger and its constituents show antioxidant activity and prevent the damage of macromolecules, caused by the free radicals/oxidative stress.

2. Ginger and its constituents also show a vital role as anti-inflammatory processes. Earlier studies on *in vitro* investigations of ginger preparations and some isolated gingerol-related compounds showed that anti-inflammatory effects of ginger such as inhibition of COX [13] and inhibition of nuclear factor kB [14].

3. Ginger also acts as antitumor via modulation of genetic pathways such as activation tumour suppressor gene, modulation of apoptosis and inhibition of VEGF. Earlier study has shown that terpenoids, constituents of ginger induce apoptosis in endometrial cancer cells through the activation of p53 [15].

4. Ginger also shows antimicrobial and other biological activities due gingerol and paradol, shogaols and zingerone. An important finding showed that 10% ethanolic ginger extract was found to possess antimicrobial potential against pathogens [16].

Pharmalogical activities of ginger and its constituents

Ginger showed its importance as a medicine in Asian countries since ancient times. Pharmalogical activities of ginger and its constituents in health managements through modulation of various biological activities described as following:

Antioxidant activity

Antioxidants are substances that play a role in the neutralization of free radicals and oxidative

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Table 1. Showing biological activities of ginger active compounds

Active compound of ginger	Biological activities	References
Gingerol and gingerol related compound	The antioxidant activity.	[90]
	Anti-tumour activity via induction of apoptosis, modulation of genetic and other biological activity.	[91-94]
	Anti-inflammatory and anti-analgesic activity.	[95]
	Anti-microbial activity.	[96]
Paradol	Hepato-protective activity.	[97, 98]
	Anti-oxidant and anti-cancerous activity.	[99-101]
Shogaol	Anti-microbial activity.	[102]
	Anti-oxidant and anti-inflammatory activity.	[91]
Zingerone	[6]-shogaol showed anticancer activities through the inhibition of cell invasion reduction of matrix metalloproteinase-9 expression, anti-proliferation activity and anti-invasion.	[52, 103, 104]
	Antioxidant activity.	[105, 106]
	Anti-inflammatory action.	[107, 108]
Zerumbone	Anti-bacterial activity.	[109]
	Anti-tumour activity.	[110]
1-Dehydro-(10) gingerdione	Anti-microbial activity.	[111]
	Regulation of inflammatory genes.	[112]
Terpenoids	Induce Apoptosis by activation of p53.	[15]
Ginger flavonoids	Antioxidant activity.	[113]

stress. The free radical production is balanced by the antioxidative defense system of our body [17]. Any alterations between reactive oxygen species (ROS) generation and its neutralization by antioxidant defense [18, 19] cause oxidative stress. Several plants and their constituents are rich source of antioxidant and play a significant role in prevention of disease progression process. Ginger is a source of a large number of antioxidants and also plays an important role in the reduction of the lipid oxidation and inhibits the pathogenesis of diseases (**Figure 3**). Previous study reported that ginger extract possesses antioxidative characteristics and shows a role in scavenge superoxide anion and hydroxyl radicals [20, 21] and gingerol, inhibited ascorbate/ferrous complex induced lipid peroxidation in rat liver microsomes [22].

The essential oil and oleoresin of *Zingiber officinale* exhibited significant antioxidant and antimicrobial activities [23]. 6-Dehydroshogaol, 6-shogaol and 1-dehydro-6-gingerdione has shown potent inhibitors of nitric oxide (NO) synthesis in activated macrophages [24]. Another report in the favor of ginger as antioxidant showed that 6-shogaol has potent antioxidant properties which can be attributed to the presence of unsaturated ketone moiety [25]. Another study has shown that phenolic substances possess strong anti-inflammatory and antioxidative properties and considerable anti-carcinogenic and antimutagenic activities [26]

and showed role as in scavenging of H_2O_2 , which donate electrons to H_2O_2 , thus neutralizing it to water [27]. Earlier report showed that antioxidative activity of ginger extract in animal model [28].

Anti-inflammatory activity

Inflammation is a complex immune process and various mediators such as interleukin-1 (IL-1), tumour necrosis factor (TNF) and anti-inflammatory cytokines involve in this process. Currently non steroidal anti-inflammatory drugs are commonly used to treat the inflammation but this drug shows an adverse side effect and gastric ulcer. Various medicinal plants and their constituents have shown a vital effect in the prevention of inflammatory process. Earlier study has shown that ginger oil (33 mg/kg), administered orally to rats for 26 days, showed significant repression of paw and joint swelling associated with severe chronic adjuvant arthritis [29]. Ginger also shows a vital role in the suppression/inhibition in synthesis of pro-inflammatory cytokines such as IL-1, TNF- α , and IL-8 [13, 30, 31]. Another finding revealed that, the elevated expression of TNF- α in liver cancer rats was blocked when treated with ginger extract (100 mg/kg body weight) [32]. In addition to that, Ginger play a role in the inhibition of COX and 5-lipoxygenase, essential for arachidonate metabolism [33], and down-regulating the induction of inflammatory genes [34, 35].

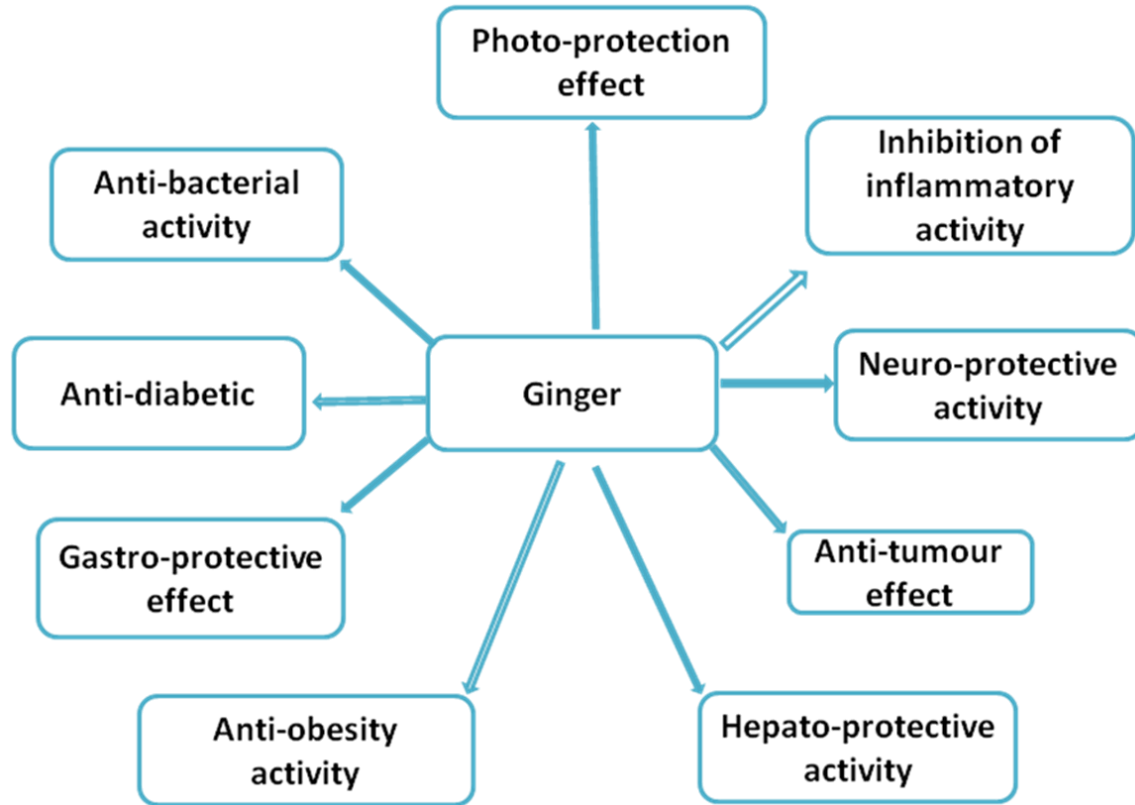


Figure 3. Ginger and its constituents shows role in diseases prevention.

Earlier investigation has shown that, Ginger root and its constituents can inhibit NF- κ B activation induced by a variety of agents [36-38] and downregulation of NF- κ B gene products involved in cellular proliferation and angiogenesis [39]. DZO also shows a role in suppressing the expression of LPS-induced IFN- γ and IL-6, which are elevated in LPS-induced inflammation [40].

Anti-tumour activity

Tumour development and progressions are multi step process including genetic and metabolic changes [41, 42]. Earlier study summarized the role of medicinal plant in the diseases management via modulation of various biological activities including cancer [43, 44]. Ginger and its constituents show a vital effect in the control of tumour development through up regulation of tumour suppressor gene, induction of apoptosis and inactivation of VEGF pathways (Figure 4). Angiogenic factor such as VEGF play a significant role in the development and progression of tumour. Therefore, Inhibition of VEGF is an important step in the prevention of

tumour development/management. Earlier investigation has shown that, 6-gingerol has role in the suppression of the transformation, hyperproliferation, and inflammatory processes that involve in various steps of carcinogenesis, angiogenesis and metastasis [45-48]. Another numerous studies showed that 6-gingerol, constituents of ginger play a role in the induction of apoptosis in the prostate cancer cell line LnCaP by increasing the expression of p53 and Bax and also decreasing the expression of Bcl-2 [49-51]. Another important study has shown that 6-shogaol show anticancer activities against breast cancer via inhibition of cell invasion reduction of matrix metalloproteinase-9 expression [52]. Another important finding suggest that 6-gingerol stimulates apoptosis through upregulation of NAG-1 and G₁ cell cycle arrest through downregulation of cyclin D1 [53].

An important study reported that ginger root extracts and gingerol play a significant role in inhibition of the growth of *Helicobacter pylori* CagA+ strains, which has a specific gene linked to the development of gastric premalignant and

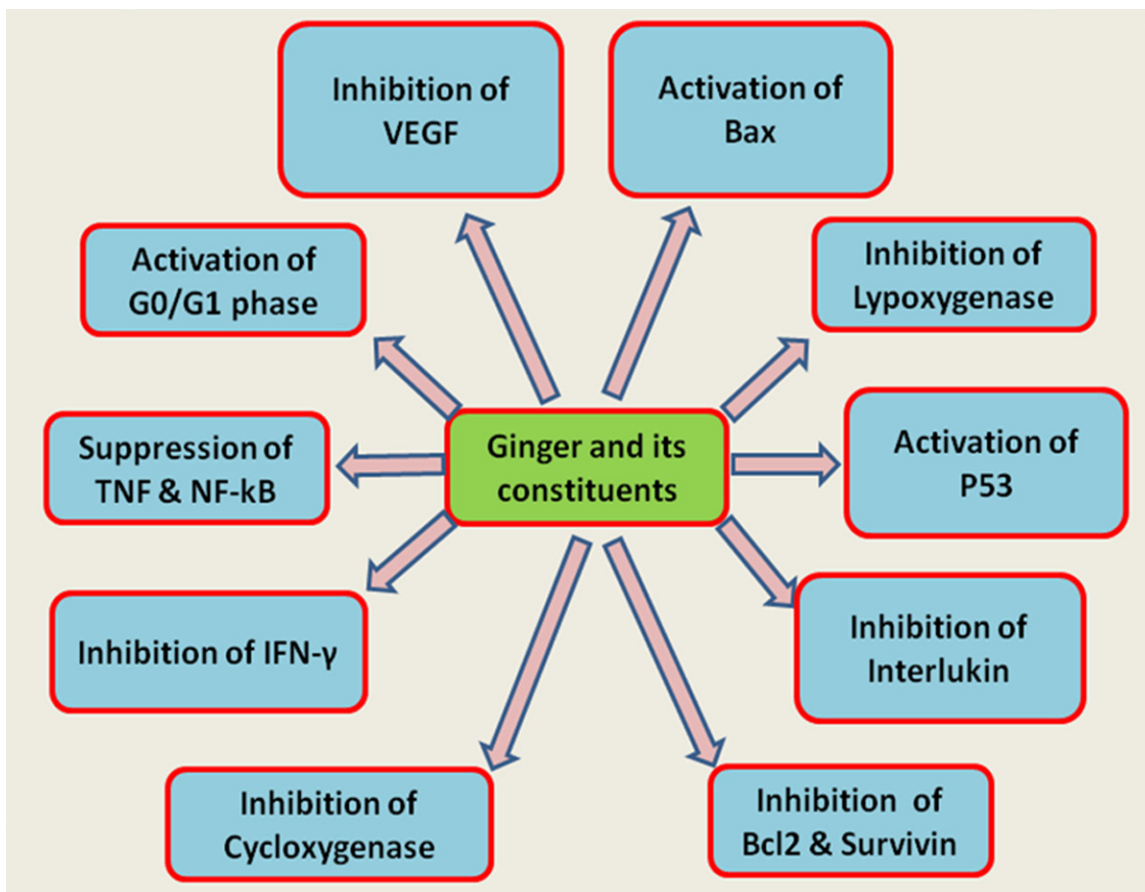


Figure 4. Ginger and its constituent play pharmacological effect in cancer management via modulation of molecular mechanism.

malignant lesions [54]. Moreover, 6-shogaol has shown to induce apoptosis in human colorectal carcinoma cells via the production of reactive oxygen species and activation of caspase [31] and [6]-gingerol inhibited pulmonary metastasis in mice bearing B16F10 melanoma cells through the activation of CD8+ T cells [55]. Earlier finding has reported that 6-gingerol showed its anti-tumoral activity through induction of ROS which is also known to trigger activation of p53 and the cell cycle arrest and apoptosis [56]. Another important and first finding showed that *in vitro* and *in vivo* anticancer activity of whole GE for the management of prostate cancer [57].

Anti-microbial activity

Drug resistance is increasing worldwide and it is considered as a main culprit in the failure of treatment. The use of antibiotics against bacteria/microorganism is an effective mode of treatment but also causes adverse complications.

Earlier investigators have shown that, ginger and its constituents play a vital role in the prevention of microbial growth or acts as anti-microbial agents. An important study in the favor of ginger as anti-microbial activity showed that ginger has antimicrobial activity against *E. coli*, *Salmonella typhi* and *Bacillus subtilis* and ethanolic extract of ginger showed the widest zone of inhibition against *Salmonella typhi* [58]. Ginger rhizome contains several constituents which have antibacterial and antifungal effects. The gingerol and shogaol are identified as more active agents [59]. Earlier studies have shown that, ginger has broad antibacterial activity and the ethanolic extract of ginger powder has pronounced inhibitory activities against *Candida albicans* [60-62] and other reports also showed that antifungal properties of ginger extract, Gingerol [63]. Chief constituents such as [6]-gingerol and [12]-gingerol, isolated from ginger rhizome, showed antibacterial activity against periodontal bacteria [64] and [10]-gingerol has been reported as

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active inhibitor of *M. avium* and *M. tuberculosis* *in vitro* [65].

Anti-diabetic activity

Diabetes is a metabolic disorder and major global health problem worldwide. It is caused by abnormality of carbohydrate metabolism which is related to low blood insulin level or insensitivity of target organs to insulin [66]. As per estimation, one person is detected with diabetes every five second in the world whereas someone dies of it every 10 second [67]. Ginger and their constituents showed pivotal role in the control of diabetes and its complications via anti hyperglycemic effect. The exact mechanism of action of ginger in diabetes control is not fully understood but it might be due to the inhibition of oxidative stress and anti-inflammatory process.

An important finding based on in STZ treated-type 1 diabetic rat model reported that, oral administration of ethanolic extract of ginger significantly decrease fasting blood glucose level [68]. Earlier study reported that significant blood glucose lowering effect of ginger juice in diabetic and non-diabetic animals [69]. Another study has shown that a significant hypoglycemic activity in rats after administration of ginger extract [70].

Neuroprotective effect

Ginger and their constituents play a vital role as neuroprotector. The exact mechanism of action of ginger in this vista is not known fully. But it is thought ginger shows neuroprotector effect due to the phenolic and flavonoids compounds. An important study has shown that, 6-shogaol has neuroprotective effects in transient global ischemia via the inhibition of microglia [71]. Another finding in the support of ginger as neuroprotector suggests that, it exhibit neuroprotective effect by accelerating brain anti-oxidant defence mechanisms and down regulating the MDA levels to the normal levels in the diabetic rats [72]. A recent report on ginger juice showed that, ginger has protective effect by decreasing the LPO and increasing GSH, SOD, CAT, GPx, GST, GR and QR and protein level in treated rats [73].

Effect on osteoarthritis

Osteoarthritis is one of the leading causes of musculoskeletal pain and disability worldwide.

Treatment of osteoarthritis based on anti-inflammatory drugs gives relief but also shows side effect and may cause gastric ulcer. Ginger shows a significant role in the treatment of osteoarthritis and also has important therapeutic importance in Ayurvedic and Unani medicine since ancient time. An important study on osteoarthritis (OA) patients of knee has revealed that, highly purified and standardized ginger extract had significant effect on reducing symptoms of OA of the knee [74]. Another report in the support of ginger showed that, ginger is effective as indomethacin in relieving symptoms of osteoarthritis with negligible side effects [75].

Gastroprotective effect

Peptic ulcer is a major problem worldwide in both sexes. Various factors including food ingredients, stress, *Helicobacter pylori* and drugs are responsible of gastric ulcer. Several medicinal plants and its constituents show anti-ulcer effect in various ways but the exact mechanism is not understood fully. Ginger and its constituents show a vital role in ulcer prevention via increasing mucin secretion. Earlier findings have shown anti-ulcerative effects of ginger in experimental gastric ulcer models [76, 77]. Chief constituents of ginger such as [6]-gingerol and [6]-shogaol suppressed gastric contraction *in situ* and suppression by the [6]-shogaol was more intensive [78].

Anti-emetic effect

Ginger and its constituents show a significant effect on nausea and vomiting. Exact mechanism of action of ginger in nausea and vomiting is not clear but it is thought that such type of effect due to constituents present in ginger including gingerols, shogaols, and galanolactone and diterpenoid of ginger [79, 80]. Studies based on animal model revealed that, ginger extract possesses antiserotonergic and 5-HT₃ receptor antagonism effects which play an important role in the etiology of postoperative nausea and vomiting [79-81]. A study in the favors of ginger role in nausea and vomiting indicating its effect and provide relief in severity in nausea and vomiting [82].

Hepato-protective effect

Earlier investigators based on experimental findings have shown that, ginger and its con-

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stituents play a significant role in hepato-protection. An important study on ginger showed its protective effect against the CCl₄-induced hepatotoxicity [83]. Another report has shown that, administration of single dose of aqueous extract of ginger (200, 400 mg/kg prior to acetaminophen) was effective in preventing the acetaminophen-induced hepatotoxicity and also decreased ALT, AST and ALP levels and increased the activities of antioxidant enzymes levels in the liver [84]. Ginger is also useful in preventing the mancozeb-induced hepatotoxicity [85]. A recent report showed that, ginger is effective in reversing lead induced reduction in the liver weight, to increase plasma SOD and CAT activity, decrease LPx [86]. A recent report summarized the role of ginger in various types of diseases including diabetic liver, kidney, eye, and neural system complications [87].

Effect on migraine

An important study showed that administration of ginger powder at dose of 500-600 mg for 3-4 days with gap of 4 hours, showed relief from migraine attack [88].

Effect of ginger on eye

Ginger and its constituents show an important role in the management of diabetes and its related symptoms including retinopathy. Earlier report has shown that an extract of ginger with dose 0.1 and 1.0 mg/mL reduced CML-KLH and MGO-derived advanced glycation end products (AGE) products by 60%-80% and glucose-derived AGE products by 50%-60% [89].

Safety, efficacy and toxicity of ginger

Numerous plants and its constituents show an important therapeutic effect in the health management. Measurement of toxicity and lethal dose level is important before using in health management. Several studies were performed to check the safe dose in animal model study. The dose and toxicity of ginger has been checked and recommended by various earlier investigators. A study in this vista, showed that dose of 0.5-1.0 g of ginger powder ingested 2-3 times for periods of 3 months to 2.5 years did not cause any adverse effects [114]. Another study on animals showed that the doses of 2.5 gram/kg body weight were tolerated without any mortality. But, when the dose was increased

to 3-3.5 gram/kg body weight then there was 10-30% mortality [115]. An important study showed that ginger extract with different dosages such as 100, 333 and 1000 mg/kg administered to pregnant rats for 10 days during the period of organogenesis caused neither maternal nor developmental toxicity [116]. Other study conducted in both male and female rats at the dosages of 500, 1000 and 2000 mg/kg body weight for 35 days and results proved that chronic administration of ginger was not associated with any mortalities and abnormalities in general conditions, behavior, growth, and food and water consumption [117].

Conclusions

Current mode of treatment based on synthetic drugs such as anti-inflammatory, anti-diabetic, chemotherapy and radiotherapy drugs for the treatment are effective but also shows adverse side effect. A safe, effective and inexpensive product is needed to control the diseases development via modulation of genetic, metabolic, anti-oxidant and other associated activity. Ginger shows an important effect in the suppression of NFκB, COX2, and LOX, induction of apoptosis, activation of tumour suppressor gene and also modulates various biological activities. Ginger and their constituents create optimism towards the novel therapeutic strategy. Future research should focus on clinical trials to investigate its effectiveness and their exact role in modulation of molecular pathways.

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