



Ginger Beer: An Overview of Health Benefits and Recent Developments

Christabel Nutakor ^{1,†}, Justice A. Essiedu ^{1,†}, Parise Adadi ^{2,*} and Osman N. Kanwugu ¹

¹ Institute of Chemical Engineering, Ural Federal University, Mira Street 28, 620002 Yekaterinburg, Russia; nutakor.christabel@gmail.com (C.N.); asiedujustice@gmail.com (J.A.E.); nabayire@gmail.com (O.N.K.)

² Department of Food Science, University of Otago, Dunedin 9054, New Zealand

* Correspondence: parise.adadi@postgrad.otago.ac.nz or pariseadadi@gmail.com

† Authors contributed equally to this work.

Received: 1 October 2020; Accepted: 25 October 2020; Published: 28 October 2020

Abstract: Since time immemorial, ginger has been widely used as a food spice, providing aromatic odor and pungent taste, and as a medicinal plant, with various therapeutic effects such as antioxidant, anti-inflammatory, and analgesic, among others. It has long been an integral constituent of most herbal medicines in Africa, China and India. Its medicinal properties are largely attributed to its outstanding amount of phenolics which include gingerols, paradols, zingerones, and many others. With consumer preference gradually and remarkably shifting from high-calorie towards low-calorie and functional beverages, the demand for ginger beer is flourishing at a faster rate. Currently, the ginger beer market is dominated by the United States. The demand for ginger beer is, however, debilitated by using artificial ingredients. Nonetheless, the use of natural ginger extract enriches beer with putative bioactive phytoconstituents such as shagaol, gingerone, zingerone, ginger flavonoids and essential oils, as well as essential nutritional components including proteins, vitamins and minerals, to promote general wellbeing of consumer. This paper presents an overview of the phytoconstituents of ginger as well as the overall biological activities they confer to the consumer. In addition, the market trend as well as the production technology of ginger beer using natural ginger extract is described here.

Keywords: beverage; ginger; phytoconstituents; volatile organic compounds; ale

1. Introduction

Prehistorically, ginger was used as a medicinal plant which is classified under the Zingiberaceae family and scientifically known as *Zingiber officinale* Roscoe, native to Asia. It is a perennial plant with yellow flowers, pseudo-stem and tuberous rhizomes called ginger or ginger root. Ginger rhizome is utilized due to its aromatic odor and pungent taste [1]. Apart from its role as food aroma or spicy, other therapeutic values such as antimicrobial, anti-parasitic, antioxidant, anti-inflammatory, analgesic, aphrodisiac, anticancer, hepato-protective, digestive aid, immune stimulating properties etc. have been associated to ginger [2]. Ginger is composed of carbohydrates, lipids, water, fibers, proteins and minerals. For centuries, ginger has been the fundamental part of most traditional herbal medicines in Africa, China and India for managing/treating ailments such as headaches, colds, osteoarthritis, muscle pains, nervous diseases, gingivitis, toothache and asthma [3]. The health benefits associated with ginger are ascribed to its outstanding amount of various phenolics compounds which include gingerols, paradols, shogaols, and zingerones [4], as well as 3-dihydroshogaols, dihydroparadols, acetylated gingerol derivatives, gingerdiols, diaryl heptanoids and ferulic acid derivatives.

It is speculated that ginger beer first originated from England in the mid-1700s and was highly patronized due to its low alcohol content. It was a common drink available even for children and considered safer than water which was frequently contaminated [5]. Moreover, a recent document revealed that the nonalcoholic and low alcohol beer (NABLAB) market has enjoyed significant growth in the past years and is forecasted to keep growing [6]. There is growing consumer demand for NABLAB with different flavors taking into consideration the health benefit from such products. One possible strategy to satisfy the consumer need is to add ginger or its extract to beer during brewing, to retain its flavor and health promoting phytochemicals. Earlier researchers have added various fruits to beer with the aim of improving the antioxidant and other health promoting factors [7–9]. A literature search on databases (Web of Science, PubMed, and Scopus) identified only two studies [10,11] with regards to the production technologies of ginger beer. Therefore, the present review aims to highlight the market trend, health benefits and production technology of ginger beer.

2. Global Market Trends of Ginger Beer (Ale)

Currently, the consumer preference is progressively shifting from high-calorie to remarkably low or less sugary alcoholic or non-alcoholic beverages. To meet these rapid demands the beverage industries across the globe had to launch novel technologies to create new sorts of beverages and thus, igniting the global market for these beverages including ginger ale, commonly known as ginger beer [12]. Ginger-based beverages have received considerable attention owing to the growing awareness of health benefits derived from these products [13]. This has ignited their demand, thus increasing market growth. According to reports the global demand for ginger beer was valued at approximately \$7.5 billion in 2018 and is anticipated to increase further to \$10.85 billion by the end of 2025 with a staggering compound annual growth rate (CAGR) of around 5.4% [12]. Another report has predicted a growth rate of 6.85% by 2025 [14]. The global market is mainly dominated by North America (largely centered on the U.S. market) which accounts for the majority of shares in 2018. The patronage in Western Europe cannot be ignored as it holds a significant portion of the global market. Nevertheless, Asia Pacific regions are projected to grow excluding Japan. Sadly, ginger beer is not popular in the Middle East and Africa [12], however, this might change in coming years if companies in these regions commence importing ginger ale.

3. Proximate Analysis of Ginger

The nutritional constituents of ginger differ base on the variety, agronomic conditions/practices, curing methods, drying, storage conditions and region of cultivation. Fresh ginger rhizome contains 12.3% carbohydrates, 80.9% moisture, 1.2% minerals, 2.4% fiber, 2.3% protein, and 0.9% fat [15]. Moreover, ginger provides minerals such as iron, calcium, and phosphorous, as well as amino acids and vitamins including thiamine, vitamin C, niacin and riboflavin [16,17] (Table 1). According to Ajayi et al. [18] the amino acid composition differs based on the type of ginger rhizome (Table 2). Potassium, manganese, and vitamin C help build resistance against disease and protect the lining of the heart, blood vessels and urinary duct. A negligible amount of vitamins A, E, B and C was reported in ginger [19]. Due to its nutritive nature, ginger has been utilized to design biofortified foods globally [20].

Table 1. Nutritional composition of ginger.

Nutrients	[15]	[20]	[21]	[21]	[22]
Moisture	15.02 ± 0.04%	13.75%	84.16 ± 0.97%	89.14 ± 0.72%	75.20 ± 0.53%
Carbohydrate	38.35 ± 0.1%	7.64%	15.39 ^a %	15.41 ^a %	2.01 ± 0.23%
Crude ash	3.85 ± 0.61 (4.53)%	NR	0.02 ^a %	0.04 ^a %	0.81 ± 0.01%
Crude fat	3.72 ± 0.03 (4.37)%	4.02%	0.09 ^a %	0.08 ^a %	11.71 ± 0.19%
Crude fiber	25.5 ± 0.04 (30.0)%	13.75%	0.17 ^a %	0.16 ^a %	1.38 ± 0.50%
Crude protein	5.087 ± 0.09 (5.98)%	34.13%	0.17 ^a %	0.15 ^a %	8.91 ± 0.04%
Sodium	NR	NR	NR	NR	7.32 ± 0.02 mg
Zinc	0.92 ± 0 (1.08) mg	64.0 mg	NR	NR	4.99 ± 0.04 mg
Calcium	88.4 ± 0.97 (104.02) mg	280.0 mg	NR	NR	182.67 ± 0.04 mg
Iron	8.0 ± 0.2 (9.41) mg	279.7 mg	NR	NR	9.68 ± 0.02 mg
Manganese	9.13 ± 0.01 (10.74) mg	5.90 mg	NR	NR	NR
Copper	0.545 ± 0.002 (0.641) mg	8.80 mg	NR	NR	NR
Phosphorus	174 ± 1.2 (204.75) mg	8068.0 mg	NR	NR	NR
Chromium	70 ± 0 (83.37) µg	NR	NR	NR	NR
Vitamin C	9.33 ± 0.08 (10.97) mg	1.036	NR	NR	NR

NR—not reported; Numbers in the parenthesis represent the dry weight values; ^a calculated by authors.

Table 2. Amino acid composition of ginger varieties.

Essential Amino Acids	White Type	Yellow Type	Non-Essential Amino Acids	White Type	Yellow Type
Lysine (Lys)	2.70	15.90	Alanine (Ala)	10.60	9.90
Arginine (Arg)	41.40	26.80	Aspartic acid (Asp)	29.80	31.60
Threonine (Thre)	9.10	23.20	Glutamic acid (Glu)	56.80	35.80
Phenylalanine (Phe)	10.00	27.40	Serine (Ser)	23.10	10.20
Valine (Val)	22.00	23.70	Proline (Pro)	15.00	8.10
Methionine (Met)	5.70	4.70	Glycine (Gly)	22.60	17.10
Isoleucine (Ile)	10.70	10.40	Cystine (Cys)	4.60	4.60
Leucine (Leu)	42.00	56.00	Tyrosine (Tyr)	11.10	14.20
			Histidine (His)	10.40	5.00

Adapted from [18].

4. Phytochemical Composition of Ginger

The phytochemical composition of ginger differs based on the geographical location where it is sourced; nonetheless, the main phytochemical constituents of ginger are shown in Table 3. Bio-active compounds such as shogaols, paradol, zingerone, gingerenone, gingerols, as well as volatile oils determine the distinct flavor of ginger. According Chrubasik, et al. [23], zingerone, gingerdiol, zingibrene, gingerols and shogaols were the active ingredients identified in ginger. Others include volatile oil (farnesene, zingiberol, D-camphor, etc.) diarylheptanoids, paradol, zerumbone, 1-Dehydro-(10) gingerdione, terpenoids and ginger flavonoids [24].

Table 3. Phenolic compounds detected in ginger.

Phenolic Compounds	WEG [25]	EEG [25]
Pyrogallol	142.4	264.3
p-Hydroxybenzoic acid	321.1	29.4
Ferulic acid	88.8	224.7
Vanillin	101.2	89.4
p-Coumaric acid	291.4	170.2
Gallic acid	29.8	39.6
Ascorbic acid	BDL	31.3
Caffeic acid	9.8	91.2
Syringic acid	BDL	BDL
Ellagic acid	BDL	BDL

Quercetin	BDL	BDL
α -Tocopherol	BDL	BDL
Catechol	BDL	BDL

WEG_Lyophilized aqueous extract of ginger; EEG_Ethanol extract of ginger; BDL_below detectable level.

According to [26], phytochemicals are plant-based secondary metabolite which exert a myriad of biological functions which include the ability to act as antioxidants, act as inflammatories, modulate enzyme activity, and regulate gene expression.

High performance liquid chromatography (HPLC) analysis of ginger varieties (Halia Bentong and Halia Bara) cultivated on soilless mixture media including burnt rice husk and coco peat (ratio 1:1) with varying light intensity revealed that the concentration of the flavonoids (quercetin, rutin, catechin, epicatechin and naringenin) increased in plants grown under $310 \mu\text{mol m}^{-2} \text{s}^{-1}$. The flavonoid of Halia Bentong variety grown under $790 \mu\text{mol m}^{-2} \text{s}^{-1}$ and $310 \mu\text{mol m}^{-2} \text{s}^{-1}$ was 3.31 ± 0.21 and 4.1 ± 0.163 , respectively. Additionally, the Halia Bara variety presented 3.83 ± 0.213 and 4.73 ± 0.08 , respectively [27]. Mošovská et al. [28] also reported total flavonoid ($14.15 \pm 0.12 \text{ mg quercetin/g}$) and phenolics ($181.41 \pm 0.07 \text{ mgGAE/g}$) in ginger extracts. According to the literature, phenolics are an important class of antioxidant due to their radical scavenging activity [25]. Ali and colleagues [29] extracted ginger rhizome and callus with petroleum ether (PE) and chloroform: methanol (1:1, *v/v*) (CM). The results revealed that the total phenolic concentration in CM extract of ginger rhizome was higher ($60.34 \pm 0.43 \text{ mg gallic acid/g}$) compared to PE extract ($52.17 \pm 2.41 \text{ mg gallic acid/g}$), but not significantly different between the treatments [29]. Using methanol, ethanol and water as solvents, Tanweer et al. [30] reported total phenolics of ginger rhizome to be 430.72 ± 16.80 , 650.44 ± 27.32 and $297.88 \pm 10.43 \text{ mg GAE/100 g}$, respectively. With respect to flavonoids an amount of 234.06 ± 9.13 , 239.52 ± 10.06 and $218.34 \pm 7.64 \text{ mg/100 g}$ was detected in methanol, ethanol and water extracts, respectively. Likewise, flavonols concentration in methanol, ethanol and water extracts were 37.48 ± 1.56 , 43.38 ± 1.74 and $32.24 \pm 1.40 \text{ mg/100 g}$, respectively [30]. Fresh ginger extracted in methanol showed the highest total phenolics ($95.2 \text{ mg/g dry extract}$) followed by hexane extract ($87.5 \text{ mg/g dry extract}$) [31]. Osabor and coworkers detected alkaloids, saponins, flavonoids and polyphenols in aqueous extracts of ginger rhizomes. Furthermore, cardiac glycosides, saponins and flavonoids were also identified in PE extracts [32]. After screening different varieties of ginger and parts, mainly the leaves, stem, and rhizome, Ghasemzadeh et al. reported total flavonoids in the leaves, stem, and the rhizome to be 5.54 ± 1.83 , 1.36 ± 0.85 , $3.66 \pm 0.45 \text{ mg quercetin/g}$, respectively, for Halia Bentong, whereas 7.05 ± 7.4 , 1.77 ± 0.75 , $4.21 \pm 0.98 \text{ mg quercetin/g}$, respectively, for Halia Bara. With regard to total phenolics Halia Bentong registered 33.0 ± 1.13 , 7.8 ± 0.65 , $10.22 \pm 0.87 \text{ mg gallic acid/g}$, respectively, in leaves, stem, and the rhizome while 39.1 ± 9.2 , 8.5 ± 0.81 , $13.5 \pm 2.26 \text{ mg gallic acid/g}$, respectively, was detected in Halia Bara [33]. Also, the phytochemical constituent (mg/100 g) of dry ginger powder was saponin (4.01 ± 0.07), cyanogenic glycoside (0.81 ± 1.05), phytin (0.28 ± 0.01), oxalate, (0.26 ± 0.002) and tannin (0.02 ± 0.00) [34].

5. Biological Activities

Results of extensive studies give much information about the bioactive compounds, biological activity (i.e., antioxidant, anticancer, antidiabetic, and so on) as well the general health benefits of ginger [35]. Some of biological activities of are elaborated below:

5.1. Antioxidant Activity

Naturally, the mammalian system generates reactive oxygen species (ROS) such as superoxide, hydrogen peroxide, hydroxyl radical, hydroxyl ion, and nitric oxide as by-products during various reactions which involve the reduction in oxygen. Usually, cells actively eliminate some of these species, but at some point, these species overwhelmed the cell's ability, thus causing oxidative stress in various cells, tissues and organs leading to several diseases [4]. Studies have shown how plant extracts containing bioactive ingredients such as polyphenols, etc., act as antioxidants by donating hydrogen atoms or electrons to neutralize ROS [28]. Ginger rhizome is overwhelmed with

antioxidants which aid to lessen lipid oxidation and diseases. The essential oils and oleoresins found in ginger displayed antioxidant activities which have been reported by various studies. 6-dehydroshogaol, 6-shogaol and 1-dehydro-6-gingerdione, present in ginger, were found to inhibit nitric oxide (NO) synthesis in activated macrophages. 6-shogaol exhibited potent antioxidant activity due to the presence of unsaturated ketone moiety [36,37]. Additionally, phenolic compounds in ginger have been reported to exhibit antioxidant activities on test subjects [37]. Aeschbach et al. [38] and Chang et al. [39] illustrated the antioxidant activity of ginger rhizome in the inhibition of lipid peroxidation by FeCl_3 with the ascorbate system and the inhibition of xanthine oxidation system, respectively. These systems are responsible for the release of ROS like superoxide anion [40]. In vitro and in vivo studies revealed that 6-shogaol rich extract from ginger enhanced the antioxidant defense mechanism by triggering the nuclear factor E2-related factor 2 (Nrf2). Interestingly, 95% of ethanolic extracts obtained at 80 °C showed better antioxidant response element pathway (ARE) reporter gene activity and Nrf2 expression in HepG2 cells than 95% ethanolic extracts obtained at room temperature [41]. Likewise, in vitro study (DPPH scavenging capacity assay) revealed that ethanol, methanol and aqueous extracts of ginger exhibit potent antioxidant activity with ethanolic extract being the most prominent ($65.30 \pm 2.74\%$) and aqueous extract being the least. The authors arrived at similar findings when they used Ferric reducing antioxidant potential (FRAP)—the maximum FRAP ability was exhibited in ethanolic extract ($102.62 \pm 4.28 \mu\text{mol TE/g}$) as compared to methanolic ($98.14 \pm 3.3 \mu\text{mol TE/g}$) and water extracts ($94.86 \pm 3.32 \mu\text{mol TE/g}$) [30].

5.2. Anticancer Activity

The formation of cancer cells is a complex process triggered by physical, chemical, viral mechanisms, genomic and epidemic alterations which ultimately lead to the malignant conversion of a normal cell. The damage of macromolecular species like lipids, proteins, polysaccharides and nucleic acid leads to dysfunction of cellular metabolism which includes lipid peroxidation and induction of oxidative stress in healthy cells. This lipid peroxidation plays a vital role in carcinogenesis and may lead to the formation of several toxic products such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). These products can attack cellular targets, thereby inducing carcinogenicity [42]. During carcinogenesis, cytokines are produced by the inflammatory cells, which promote the survival, growth, mutation, proliferation, and differentiation of tumor cells [43]. Habib et al. [43] studied the effect of ginger extract on cancer cells and found that the extract had a chemotherapeutic effect on infected cells. Similarly, a recent study has shown the chemopreventive effect of ginger against 7,12-dimethylbenz [a] anthracene-related skin tumors. Ginger anticancer properties are credited to 6-gingerol, 6-paradol, shogaols and zingerone constituents which inhibit cyclooxygenase and lipoxygenase activities, initiates apoptosis and elicits an antitumorigenic effect. Therefore, ginger has the potential of being used in cancer therapy to induce cell death in leukemic, skin, kidney, lung and pancreatic cancer cells [44]. Moreover, gingerol was potent in blocking cyclooxygenase-2 (COX-2) expression by inhibiting p38 MAPK–NF- κ B (mitogen activated protein kinase—necrosis factor kappa B) signaling pathway [40,45]. Similarly, an in vitro study revealed that 6-Shogaol suppressed growth of ovarian cancer cells by inhibiting NF- κ B activation as well as growth factor (VEGF) and IL-8 secretion [45,46]. A conventional anticancer drug β -elemene developed from ginger extract was effective in managing patients suffering from lung cancer [47]. In addition, ginger supplements boosted glutathione reductase (GR), glutathione peroxidase (GPX), and glutathione -S-transferase (GST) which led to the inhibition of colon cancer [44]. Table 4 summarizes some potential anticancer mechanism of ginger and its components reported in various studies.

Table 4. Anticancer activity of ginger.

Compound Name	Cancer	Mechanism	Cell Lines/System	References
Ginger extract	Liver cancer	Reduced the elevated expression of TNF- α and NF- κ B	Rats	[43]
Ginger—whole and [6]-gingerol	Ovarian cancer	Inhibition NF- κ B and tumor growth	In vitro	[46]
β -Elemene	non-small-cell lung cancer cells	Release of cytochrome c	In vitro	[47]
6-gingerol	Breast cancer	Inhibits cell adhesion invasion motility	In vitro	[48]
	Skin cancer	Enhances apoptosis	Mouse	[47]
	Colon cancer	Inhibition of leukotriene activity	Mice	[49]
Zerumbone	Lung and colon cancer	Suppresses modulatory mechanisms of growth and induces apoptosis. Reduces expression of NF- κ B	Mouse	[50]
	Colon cancer	Activation of extracellular signal-regulated kinase 1/2 p38 mitogen-activated protein kinase	In vitro	[51]
	Osteoclastogenesis.	Blocks NF-kappa B expression.	Mouse monocyte	[52]
6-Shogaol	Lungs cancer	Inhibition of AKT	In vitro	[53]
6-Shogaol	Breast cancer	Anti-metastasis	In vitro	[54]
Enone-diaryl heptanoid, 6-Shogaol, [10]-gingerol,	Liver/against nine human tumor cell (lines)	Inhibition of lipid peroxidation, Antioxidant activity, cytotoxic	In vitro	[55]
Terpenoids	Endometrial Cancer Cells	Induces apoptosis by activation of p53	In vitro	[56]
6-Shogaol	Cancer cell	Anticancer	In vitro	[57]

Modified from [45].

5.3. Antidiabetic Activity

Diabetes is a chronic disease marked by high levels of blood glucose or sugar (hyperglycemia) [58]. By numerous biochemical and physiological control mechanisms, the body maintains a constant blood glucose concentration within homeostatic state. A hormone called insulin synthesized in the pancreas (specifically by the β cells) regulates carbohydrate metabolism in the body and maintains the flow of glucose across cell membranes [59]. Diabetes occurs either by less or no production of insulin by the β cells (type 1) or as a result of insulin resistance (where insulin is synthesized but not functional due to a diminished response of tissues to insulin—type 2). Pregnancy, surgery, medication, hormonal dysfunction etc. may alter the level of blood glucose [60]. Numerous studies have examined the efficacy of ginger and its extracts in hyperglycemia control in both in vivo and in vitro trials. Li et al. outlined the various mechanisms involved in the antidiabetic activity of *Zingiber officinale*:

1. Ginger inhibits prominent enzymes associated with hyperglycemia in the carbohydrate metabolism (that is α -amylase and α -glucosidase).
2. Additionally, ginger enhances insulin release by β cells and sensitivity by promoting glucose clearances in insulin responsive peripheral tissues to aid in maintaining blood glucose homeostasis.
3. Finally, ginger improves lipid profile with its prominent lipid lowering effect [61].

Other reports [62,63] showed that ginger extract exerted small but relevant blood glucose—lowering potentials in diabetic and non-diabetic animals. Oboh et al. [63] speculated that ginger is a good source of water-extractible phytochemical which can inhibit enzymes linked to type 2 diabetes. In an in vivo study using a streptozotocin (STZ)-induced type I diabetes, Akhiani et al. [64] showed that ginger extract significantly decreases glucose levels and increase insulin in STZ-diabetic rats. Also, treatment decreased serum cholesterol, triglyceride and blood pressure in diabetic rats [64]. Orally feeding STZ-induced diabetic mice with ethanolic extract of ginger (200 mg/kg) for 20 days showed antihyperglycaemic effect ($p < 0.01$) on diabetic rats. In addition, treatment lowered the serum's total cholesterol, triglycerides and increased the high-density lipoprotein (HDL)-cholesterol levels compared with pathogenic diabetic rats ($p < 0.01$). Liver and pancreas thiobarbituric acid reactive substances (TBARS) values ($p < 0.01$) were also lowered in the treated group compared to the pathogenic diabetic rats. The results were comparable to the group treated with the reference drugs gliclazide (25 mg/kg, orally) [65]. Similarly, a significant ($p < 0.05$) decrease occurred in the serum glucose level of alloxan-induced diabetic rats after treatment with ginger extract (500 mg/kg BW). However, the blood glucose level of the control and diabetic rats remained unaltered [59]. Chukwudike and Mercy [66] documented a promising result where doses of 250, 500 and 1000 mg/kg b.w ginger extracts significantly lowered blood glucose levels to 120.83 ± 2.1 , 89.8 ± 8.2 , 90.5 ± 4.2 mg/dL in diabetes-induced (alloxan monohydrate solution; 150 mg/dL, intraperitoneally) male Wistar rats, respectively, compared to the control 168.2 ± 1.8 mg/dL.

Treating streptozotocin-induced diabetic (45 mg/kg body) Wistar Albino rats weighing between 150 and 200 g with either green tea or ginger extract and a combination further showed the sugar lowering potential of ginger. Green tea and ginger extract significantly decreased blood glucose from 176.5 ± 20 , 210 ± 8.5 to $80 \pm$ and 5.582 ± 14.7 mg/dL, respectively, whereas their combination exerted the highest hypoglycemic from 220 ± 8.5 to 59.1 ± 11.7 mg/dL when compared to diabetic rats (from 200.5 ± 25.5 to 187.3 ± 37.6) [67].

A recent randomized double-blinded placebo-controlled trial of ginger on gestational diabetic patients with impaired glucose tolerance test (GTT) revealed that treatment significantly decreased the fasting blood sugar (FBS; $p = 0.004$) level, serum insulin ($p < 0.001$) and Homeostatic model assessment (HOMA) index ($p < 0.001$) compared to the placebo group which showed no significant difference. Therefore, oral administration of ginger tablets can be used to manage gestational diabetes mellitus (GDM) in pregnant women [68]. Similarly, Rafie and colleagues reported a significant decrease in fasting blood sugar in groups that received ginger supplements compared to the placebo group. In contrast, no significant difference was observed in either group with regard to fasting, insulin, low-density lipoprotein (HDL-C), triglyceride, adiponectin, alpha-tumor necrosis factor (TNF- α), total antioxidant capacity (TAC), gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), fatty liver index (FLI), fatty liver grade and blood pressure [69]. Shidfar et al. also found that consuming 3 g of powdered ginger daily for 3 months significantly lowered the blood glucose (-19.4 ± 18.8 mg/dL) of diabetic patients compared to the control (1.6 ± 4.2 mg/dL). Other serum biochemical variables such as HbA1c percentage (-0.77 ± 0.88), insulin (-1.46 ± 1.7 μ IU/mL $p < 0.001$), insulin resistance (-16.38 ± 19.2 , $p < 0.001$), high-sensitive CRP (-2.78 ± 4.07 , mg/L, $p < 0.001$), paraoxonase-1 (PON-1) (22.04 ± 24.53 U/L, $p < 0.006$), TAC (0.78 ± 0.71 μ IU/mL, $p < 0.01$) and MDA (-0.85 ± 1.08 μ mol/L, $p < 0.001$) differed significantly in the treated group [70].

5.4. Anti-Hypercholesteremic Effect

Hypercholesteremia is a condition where there is a rise in the level of cholesterol and low-density lipoprotein (LDL) in the plasma and is linked with mutation of genes such as encoding low-density lipoprotein receptor (LDLR), encoding apolipoprotein B (APOB), etc. [71]. It is inherited genetically as an autosomal dominant syndrome which can cause xanthomas, arcus corneae, and premature coronary heart disease [72]. A significant reduction in total cholesterol and low-density lipoprotein (LDL-C) was reported after administering ginger supplement to patients compared to the placebo group [69]. Additionally, oral administration of aqueous ginger infusion (100, 200 and 400 mg/kg) to hypercholesterolaemia-induced rats showed a significant reduction in serum cholesterol by 63.72,

60.78, 59.41% and by 70.85, 69.41, 77.46% after 2 and 4 weeks of treatment, respectively, compared to the positive control (atorvastatin at dose of 0.18 mg/kg) by 51.04 and 69.04%. With respect to serum triglyceride levels, the same dose mentioned above manifested a significant reduction by 34.01, 73.6, and 74.76% and by 42.53, 84.28, and 90.49%, respectively, after 2 and 4 weeks of treatment compared to the positive control which also exhibited a significant reduction by 43.41 and 76.79% after 2 and 4 weeks of treatment, respectively [73]. Elevated serum cholesterol level in hypercholesterolemia-induced rabbits, by feeding them 0.5 g cholesterol in 5 mL hydrogenated vegetable oil, decreases significantly by administering ethanolic ginger extract (200 mg/kg, p.o.). The reduction was similar when reference drugs gemfibrozil was used. In addition, serum triglycerides, very low-density lipoproteins (VLDL-C), and serum phospholipids decreased significantly, but not high-density lipoprotein (HDL-C). The author speculated that phytochemicals in the extracts may have triggered transformation of cholesterol to bile acids [74]. Thomson et al. [75] also reported a significant decrease in serum prosta-glandin-E2 (PGE2) when hypercholesterolemia rats were orally fed with aqueous extract of ginger (50 mg/kg). The higher dose (500 mg/kg) was potent in lowering PGE2 and thromboxane-B2 (TXB2). The lower dose had no effect on TXB2 synthesis. Neither dose was sufficient to alter the serum's triglyceride levels [75].

5.5. Anti-Inflammatory Effect

Sharma et al. [76] examined the anti-inflammatory activity of ginger oil (33 mg/kg) by injecting a suspension of dead mycobacterium tuberculosis to induce severe arthritis in male Sprague-Dawley rats. The oil significantly reduced the paw and joint swelling compared to the control and group treated with eugenol [76]. Similarly, ginger essential oils (28 mg/kg/d) suppressed chronic joint inflammation by 38% in streptococcal cell wall (SCW)-induced arthritis in a female Lewis rat [77]. Yong-liang and colleagues [78] also found that ginger oil (0.25–1.0 g/kg) produced dose-dependent significant repression of the carrageenan-induced paw edema, adjuvant arthritis, and inflammatory mediators-induced vascular permeability in Male Sprague-Dawley rats ($p < 0.05$, 0.001). However, aspirin (0.5 g/kg) exhibited efficient anti-inflammatory activity compared to the ginger oil (0.5 g/kg) [78]. Table 5 shows extensive studies on anti-inflammatory potentials of ginger bioactive compounds.

Table 5. Anti-inflammatory activity and potential mechanisms of ginger.

Constituent	Study Type	Subjects	Dose	Potential Mechanisms	Ref.
6-shogaol	In vitro	HT-29/B6 and Caco-2 human intestinal epithelial cells	100 μ M	Inhibiting the PI3K/Akt and NF- κ B signaling pathways	[79]
6-shogaol and 6-gingerol, 6-dehydroshogaol	In vitro	RAW 264.7 mouse macrophage cells	2.5, 5, and 10 μ M	Inhibiting the production of NO and PGE2	[80]
6-gingerol-rich fraction	In vivo	Female Wistar rats	50 and 100 mg/kg	Increasing the levels of myeloperoxidase, NO, and TNF- α	[81]
GDNPs 2	In vivo	Female C57BL/6 FVB/NJ mice	0.3 mg	Increasing the levels of IL-10 and IL-22; decreasing the levels of TNF- α , IL-6, and IL-1 β	[82]
Ginger extract and zingerone	In vivo	Female BALB/c mice	0.1, 1, 10, and 100 mg/kg	Inhibiting NF- κ B activation and decreasing the level of IL-1 β	[83]
Ginger extract	In vivo	C57BL6/J mice	50 mg/mL	Inhibiting the production of TNF- α ; Activating Akt and NF- κ B	[84]

NO, nitric oxide; PGE2, prostaglandin E2; TNF- α , tumor necrosis factor α ; GDNPs 2, nanoparticles derived from edible ginger. Adapted from [81].

6. Toxicological Aspect and Health Concern

Ginger rhizome and their products are Generally Recognized as Safe (GRAS) [85]. Chukwudike and Mercy [66] reported that administering ginger extract at a dose from 250 to 1000 mg/kg body weight per oris did not manifest any concerns, thus no mortality was recorded. During the 28 days of the evaluation, all the rats were active, alive and healthy [66]. Similarly, Wilkinson orally fed pregnant Sprague-Dawley rats with either 15 g/L, 20 g/L or 50 g/L aqueous extract of ginger rhizomes. The author observed no signs of toxicity in treated rats. In addition, the treated group showed similar total weight gain before, during, or after treatment as the control. Nonetheless, though ginger tea may increase early embryo loss it paradoxically increases growth in surviving fetuses [86]. Thus, the amount of ginger or their product consumed must be taken with caution, especially by pregnant women. Weidner and Sigwart [87] examined the teratogenicity of EV.EXT 33 (a patented ginger extract) at different concentrations (100, 333, and 1000 mg/kg) on Wistar SPF rats (Mol. Wist). The results revealed that EV.EXT 33 exert no toxic effect on all the parameters examined even under a daily dose of up to 1000 mg/kg body weight [87]. Rong et al. [88] also carried out an acute toxicity study of ginger on rats and the results revealed oral administration of ginger powder up to 2000 mg/kg did not manifest any mortalities or abnormalities in general conditions, behavior, growth, food and water consumption of the treated rats. Evidently, hematology and blood biochemistry of treated rats were not altered except a decrease in LDH in male rats which were similar to the control group. Necropsy analysis showed that all of the examined organs except the testes of rats treated by 2000 mg/kg of ginger are normal [88]. Acute toxicity analysis of fixed (0.02, 0.04, 0.06, 0.08 and 0.1 mL/kg body weight) and essential or volatile (0.2, 0.4, 0.6, 0.8, 1.0, 2.0, 4, 6, 8 and 10 mL/kg body weight) ginger oils revealed that rats treated with 0.2 mL/kg fixed oil died. Similarly, six out of the ten treated (with essential oils) rats survived. The authors found that ginger oil at a concentration of 0.002 mL/kg body weight altered the liver tests, AST and alkaline phosphatase (ALP) compared to the control (fed with corn oil) [89]. Jeena et al. [90] reported that treatment of ginger oil at doses of 100, 250, and 500 mg/kg per day for 13 weeks had no toxicity effects on rats. The no-observed-adverse-effect level (NOAEL) proposed was 500 mg/kg per day [90]. Different food spices which include ginger, clove, black pepper, red pepper in combination with lemon grass supplementation and a control (lemon grass) were fed to rats at different concentration. The results showed weight gain with regards to rats fed with ginger among other spices. A contrast group treated with the combination of all the spices (ginger, clove, black pepper, red pepper, lemon grass) lost weight. Histological analysis revealed that liver biomarkers were altered in the group treated with lemon grass in combination with all spices, clove, ginger black pepper and red pepper compared to the control group [91]. Thus, ginger and other food spices may be toxic at certain a concentration.

7. Production Technology of Ginger Beer

Ginger beer could be either brewed by the traditional fermentation using the native microflora (probiotic) already present in ginger or by a controlled fermentation which involves the pitching *Saccharomyces cerevisiae* [92]. The natural fermentation produces beverages with inconsistent qualities (i.e., aroma, foaminess, etc.). The quality of beer has always been attributed to the yeast, malt, and fermentation conditions among others.

An amount of milled malt is mixed with hot water (67 °C) in a mash tun for 60 min. The mash is stirred at a predetermined time to enhance the conversion of starch into fermentable sugars. The temperature is subsequently increased to 75 °C for 10 min to inactivate the malt enzymes (i.e., amylase, proteases, etc.). The mash is then allowed to cool and filtered to obtained wort. The spent grains could either be used to feed animals or as raw material for extracting valuable bioactive compounds of human health benefits. The wort is boiled for 45 min, where bitter hops are added at the beginning of the boiling process. The wort is clarified by a whirlpool and allowed to cool down to 15 °C, the trub discarded [7,11,93–96]. The wort is diluted to lower the gravity (Plato) when NABLAB is to be brewed. However, earlier researchers brewed beer with fruits [7–9] and reported high alcohol content (% ABV), hence the reason to lower the wort gravity. Ginger extract could be

obtained by sorting and cleaning raw ginger (finely chopped) before extracting juice, either by boiling or pressing. The extract is added into the low-density wort, aerated with the aid of aeration stones or other means. A certain concentration of yeast (cells/mL) is pitched and fermentation carried out at 20 °C for limited days. The fermentation trub is discarded and the green ginger beer transferred into a new fermenter with a small amount of sugar for secondary fermentation (conditioning) (Figure 1).

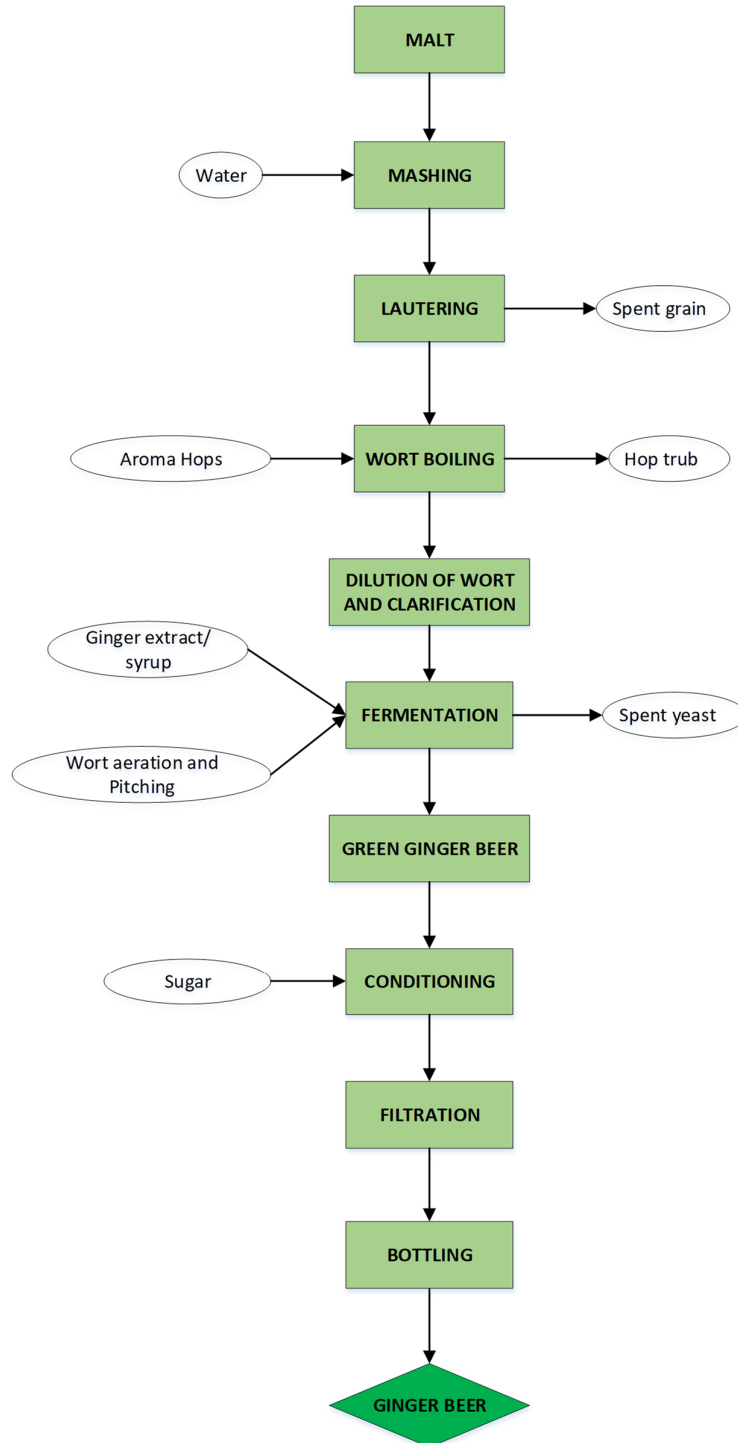


Figure 1. Production flow chart of ginger beer.

Ginger extract could be added into the green beer during conditioning [97]. The secondary fermentation could last for a week at a lower temperature. The product is then ready for bottling and consumption. Liu and colleagues developed unfermented ginger beverages by mixing ginger juice (14.57 g), sugar (6.05 g), and ginger oil (0.0034 g) in 100 g pure water. The beverage was divided into four parts for treatments; 1. without sterilization; 2. sterilized by Ultrahigh-temperature sterilization (UHT); 3. atmospheric pressure sterilization (AP); and 4. high-pressure sterilization (HP) and denoted by G1, G2, G3 and G4, respectively [98]. However, with regards to fermented ginger beer, sterilization will not be necessary since it is a product of fermentation and overwhelmed with acids in addition to alcohols which inhibits spoilage microorganisms.

The majority of ginger beers in the market are produced from carbonated water, sugar, ginger extract/syrup/flavors, citric acid, yeast, preservatives and ascorbic acid.

8. Composition of Volatile Organic Compounds (VOCs) in Ginger

The volatile compounds in ginger are numerous and most are yet to be classified. Gingerol is a common compound in ginger, which is known to be in the same family as capsaicin in chilies, and it is responsible for the characteristic burning taste of the fresh ginger. Gingerol is a yellow liquid which has a low boiling point and transformed to Shogaol upon the application of heat. The pungency in dried ginger is as a result of shogaols, zingerone, gingerone, etc [99]. Though they are present in fresh ginger, their concentration is meager compared to that in dried ginger. Zingerone is less pungent but exerts a sweet-spicy aroma in ginger. In addition, sesquiterpenoids, curcumin and diasyleheptanoids are also present in smaller amounts [19].

El-Ghorab et al. [31] reported that the major VOCs in fresh ginger essential oil were camphene (15.9%), α -terpineol (8.8%), farnesene (8.8%), p-cineole (8.4%), β -myrcene (7.7%), pentadecanoic acid (7.9%), zingiberene (7.5%), geranyl isobutyrate (5.8%), 3,7-dimethyl-1,3,7-octatriene (5.7%), 9,12-octadecadienal (4.9%), 9,12,15-octadecatrienal (4.6%), nerolidol (4.4%) and α -phellandrene (3.9%). On the other hand, camphene (14.1%), α -terpineol (10.9%), p-cineole (9.4%), 9,12,15-octadecatrienal (9.1%), zingiberene (8.4%), pentadecanoic acid (8.0%), farnesene (7.5%), geranyl isobutyrate (7.0%), limonene (3.3%), 9,12-octadecadienal (2.9%), 3,7-dimethyl-1,3,7-octatriene (1.9%), nerolidol (2.0%) and α -phellandrene (1.0%) were detected in dried ginger. Similarly, Yang, et al. [100] compared three different extraction techniques including headspace solid-phase microextraction (HS-SPME), petrol ether extraction (PEE) and steam distillation extraction (SDE) for gas chromatography-mass spectrometry (GC-MS) of volatile constituents from ginger. The results revealed camphene (1.1%), myrcene (0.2%) β -phellandrene (3.3%), curcumene (4.9%), zingiberene (53.1%), farnesene (8.6%), β -bisabolene (6.0%), and β -sesquiphellandrene (13.0%) as the major volatiles detected by HS-SPME-GCMS, whereas camphene (3.0%), myrcene (0.6%), β -phellandrene (9.1%), curcumene (4.7%), zingiberene (39.0%), farnesene (7.6%), β -bisabolene (5.9%), and β -sesquiphellandrene (13.0%) were VOCs identified by PEE-GCMS. With regard to SDE-GCMS the VOCs reported were camphene (5.7%), myrcene (1.0%), β -phellandrene (15.1%), cineole (1.7%), (E)-citral (1.1%), curcumene (4.5%), zingiberene (35.1%), farnesene (6.5%), β -bisabolene (5.2%), and β -sesquiphellandrene (10.4%). The major VOCs reported in ginger oil are camphene, p-cineole, geranyl isobutyrate, zingiberene, R-terpineol, farnesene, β -myrcene and α -phellandrene [101]. Höferl and colleagues documented detailed VOCs in ginger rhizome essential oil [102].

Volatile Characteristics of Ginger Beverages

A total of 53 VOCs was identified in unfermented ginger beverage by solid phase microextraction (SPME) GC-MS. Among the VOCs identified, 25 were alcohols, 16 terpenes, 9 aldehydes, 5 ketones, 3 esters and 1 acid (Table 6) [98]. According to Ding et al., alcohols and aldehydes significantly influenced ginger aroma, and imparts fruity, floral, gingery, and sweet notes [103], therefore could elicit similar aroma characteristics to ginger beer. Alcohol is a precursor for ester synthesis in addition to acyl-coenzyme A and alcohol acyltransferases. Esters are sweet fruity-flowerly, candy and perfume-like aromas, synthesized in trace quantities, yet are the most important

flavor in beverages [104–106]. However, few esters were detected [98] because the formulated beverage was not fermented, hence the necessary enzymes (from yeast) required to initiate ester synthesis were absent. Pinho et al. reported that volatile acids impart vinegary, mushy, and fatty smells to beverages [107]. Surprisingly, only one acid was detected [98]. According to the literature [108–110], terpenes are mostly originated from the resins and essential oils found in the bright yellow lupulin glands of flowering plants (i.e., hops). Richter et al. reported that terpenes, despite accounting for a small percentage of the overall sensory profile, played an important role in the flavor and aroma in beer [111]. Similarly, using different methods, namely headspace sorptive extraction (HSSE), stir bar sorptive extraction (SBSE), HS-SPME and solvent-assisted flavor evaporation (SAFE), 16 terpenes were detected in beer [112]. These VOCs are typically present in conventional beers [7,93] and other food condiments [113] and impart a pungent aroma to the products. According to a recent study, these flavors influence consumers' acceptance and patronage of products [95]. However, beer flavor is the result of the interaction between many chemical compounds and their perception of taste and olfactory receptors [114]. Analysis of variance of sensory evaluation of unfermented ginger beverage showed a significant difference between samples ($p < 0.001$) with regard to attributes (fruity, gingery, piquant, and cooked) indicating that the processing method influenced flavor intensities (Table 7). With regard to the fruity note, G1 was significantly different compared to G2, G3, and G4. Notably, no significant difference was register for floral note. However, G1, G3 and G4 were statistically different from G2 in term of the gingery note. All samples differed with regard to cooked notes [98] which may be attributed to the sterilization methods used. AP and HP led to significant loss of VOCs [98] which goes to support previous results [103]. On the other hand, the control and UHT samples retained most aroma from ginger. In terms of taste, specifically Piquant note, G1 and G3 were statistically different from G3 and G4. Surprisingly, treatment elicited no significant effects on sweet and sour notes of samples [98].

Tozetto and colleagues reported the sensory acceptability index values of beer supplemented with ginger juice as 95%, 90%, 90%, 86%, 96% and 92% for color, taste, aroma, bitterness, appearance and global acceptance, respectively [11]. Similarly, Husain et al. assessed the sensory attributes of "Sarabba Instan" a traditional "Bugis-Makassar" beverage produced from "Enrekang" or "Sunti" or "Emprit" ginger. The level of preference for the products was as follows for lecturers (90.91%), staff (85.72%) and students (66.68%) [115].

Table 6. Concentration of volatile compounds detected in four different ginger flavored beverage.

Code ^a	RI ^b	Compound	Area Ratio of the Compounds to the IS Compound ^c			
			G1	G2	G3	G4
Terpene hydrocarbons						
1	958	Camphene	ND	ND	ND	0.373 ± 0.007
2	974	Sabinene	0.182 ± 0.003	0.175 ± 0.003	0.231 ± 0.003	0.838 ± 0.002
3	987	β-Myrcene	ND	0.104 ± 0.003	ND	0.334 ± 0.007
4	998	α-Phellandrene	ND	ND	ND	0.222 ± 0.003
5	1040	(E)-β-Ocimene	0.490 ± 0.104	0.263 ± 0.033	0.513 ± 0.024	0.348 ± 0.044
6	1052	α-Terpinene	ND	0.127 ± 0.007	0.220 ± 0.004	0.479 ± 0.001
7	1340	δ-Elementene	0.321 ± 0.004	0.659 ± 0.001	0.458 ± 0.003	0.303 ± 0.001
8	1475	(Z)-2,6-dimethyl-2,6-octadiene	0.610 ± 0.008	0.659 ± 0.003	0.743 ± 0.004	0.903 ± 0.001
9	1482	α-Curcumene	1.064 ± 0.008	0.714 ± 0.003	0.570 ± 0.006	0.948 ± 0.014
10	1493	Valencene	ND	ND	0.389 ± 0.002	ND
11	1496	β-Selinene	ND	0.385 ± 0.007	0.208 ± 0.003	0.382 ± 0.002
12	1498	Zingiberene	12.519 ± 0.083	4.886 ± 0.003	7.081 ± 0.006	4.406 ± 0.014
13	1510	(E,E)-α-farnesene	1.664 ± 0.002	0.198 ± 0.003	1.058 ± 0.002	0.376 ± 0.002
14	1526	β-Sesquiphellandrene	7.667 ± 0.170	4.855 ± 0.081	4.970 ± 0.038	3.635 ± 0.036
15	1540	α-Cadinene	0.227 ± 0.002	0.384 ± 0.003	0.273 ± 0.002	0.419 ± 0.001
16	1557	Epoxyalloaromadendrene	0.206 ± 0.001	0.340 ± 0.002	0.263 ± 0.002	0.286 ± 0.003
Alcohols						
17	902	2-Heptanol	ND	0.185 ± 0.003	0.214 ± 0.001	ND
18	1017	(E)-2-Caren-4-ol	0.340 ± 0.003	0.340 ± 0.002	0.295 ± 0.001	0.321 ± 0.003
19	1088	L-Linalool	2.089 ± 0.024	1.963 ± 0.019	2.301 ± 0.021	1.970 ± 0.011

20	1105	2-Nonanol	0.706 ± 0.008	0.404 ± 0.003	0.637 ± 0.001	0.537 ± 0.006
21	1147	Eucalyptol	3.580 ± 0.010	2.794 ± 0.019	4.684 ± 0.008	4.231 ± 0.045
22	1167	Borneol	3.260 ± 0.022	2.634 ± 0.041	3.564 ± 0.019	3.801 ± 0.014
23	1177	α-Terpineol	5.811 ± 0.043	5.860 ± 0.034	4.983 ± 0.029	4.178 ± 0.024
24	1198	Myrtenol	0.246 ± 0.002	0.239 ± 0.003	0.253 ± 0.003	0.263 ± 0.007
25	1203	Isopulegol	0.263 ± 0.003	0.477 ± 0.004	0.312 ± 0.001	ND
26	1230	Nerol	ND	0.201 ± 0.008	ND	ND
27	1250	Geraniol	0.674 ± 0.012	1.453 ± 0.102	0.533 ± 0.003	0.576 ± 0.012
28	1359	α-Farnesol	1.430 ± 0.007	1.079 ± 0.021	0.971 ± 0.017	0.981 ± 0.008
29	1429	3-Cyclohexen-1-ol, 4-methyl-1-(1-methylethyl)	1.156 ± 0.015	1.019 ± 0.008	1.294 ± 0.007	1.108 ± 0.018
30	1522	Agarospireol	1.281 ± 0.011	2.394 ± 0.007	2.686 ± 0.012	2.808 ± 0.009
31	1529	β-Bisabolol	2.442 ± 0.026	2.325 ± 0.021	2.645 ± 0.025	2.782 ± 0.035
32	1551	Elemol	1.393 ± 0.005	1.193 ± 0.013	0.939 ± 0.025	1.138 ± 0.011
33	1557	Citronellol	2.214 ± 0.029	1.154 ± 0.016	1.974 ± 0.016	1.743 ± 0.025
34	1560	(E)-Nerolidol	2.257 ± 0.005	1.928 ± 0.003	1.634 ± 0.003	1.401 ± 0.012
35	1573	6-Camphenol	ND	0.321 ± 0.028	0.210 ± 0.012	0.294 ± 0.003
36	1583	Zingiberenol	0.475 ± 0.004	0.943 ± 0.001	0.558 ± 0.003	1.446 ± 0.002
37	1584	Spathulenol	ND	0.198 ± 0.005	0.263 ± 0.009	0.994 ± 0.006
38	1614	β-Eudesmol	5.479 ± 0.029	4.802 ± 0.135	4.517 ± 0.081	5.544 ± 0.031
39	1625	Cedren-9-ol	0.669 ± 0.004	0.745 ± 0.001	0.384 ± 0.003	0.570 ± 0.002
40	1631	α-Acorenol	0.199 ± 0.002	ND	ND	0.224 ± 0.007
41	1650	Cubenol	1.787 ± 0.008	1.471 ± 0.013	1.490 ± 0.007	1.393 ± 0.010
Ketones						
42	1144	Camphor	0.325 ± 0.002	0.942 ± 0.003	0.436 ± 0.008	0.384 ± 0.003
43	1236	5-Hepten-2-one,6-methyl-	1.965 ± 0.028	1.864 ± 0.054	2.518 ± 0.022	2.508 ± 0.029
44	1421	2-Undecanone	0.377 ± 0.022	0.373 ± 0.016	0.271 ± 0.008	0.376 ± 0.017
45	1425	7-Decen-2-one	0.433 ± 0.003	0.113 ± 0.001	0.392 ± 0.012	ND
46	1541	β-Ionone	0.327 ± 0.005	0.455 ± 0.027	0.277 ± 0.019	0.260 ± 0.013
Aldehydes						
47	1001	Octanal	0.185 ± 0.007	0.140 ± 0.003	0.204 ± 0.003	0.277 ± 0.001
48	1208	2-Thujenal	ND	ND	ND	0.411 ± 0.017
49	1244	Neral	0.181 ± 0.007	0.330 ± 0.001	0.204 ± 0.003	ND
50	1273	Geranial	19.574 ± 0.167	18.836 ± 0.141	20.502 ± 0.109	21.145 ± 0.177
51	1295	(E)-2-Octenal	0.486 ± 0.019	0.138 ± 0.017	0.457 ± 0.010	0.417 ± 0.004
52	1322	Furfural	0.309 ± 0.058	0.330 ± 0.027	0.244 ± 0.021	0.365 ± 0.011
53	1332	Citronella	0.454 ± 0.002	0.256 ± 0.002	ND	ND
54	1452	Myrtenal	0.435 ± 0.004	0.242 ± 0.005	0.442 ± 0.002	0.440 ± 0.004
55	1460	(Z)-2-Decenal	ND	0.306 ± 0.008	ND	ND
Acids						
56	1876	Hexadecanoic acid	0.247 ± 0.002	0.173 ± 0.003	0.212 ± 0.003	0.187 ± 0.002
Esters						
57	1410	Bornyl acetate	0.587 ± 0.007	0.246 ± 0.008	0.546 ± 0.013	0.550 ± 0.004
58	1550	Neryl acetate	0.943 ± 0.014	0.178 ± 0.009	0.425 ± 0.003	0.554 ± 0.006
59	1805	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl)ester	ND	ND	ND	0.263 ± 0.008
Total			89.529	74.771	81.449	80.692

^a Codes representing the 59 volatile compounds detected; ^b RI: Retention indices determined by using a series of hydrocarbons on the DB-WAX column; ^c Area ratio of the compounds to the IS compound = peak area of a component in ginger/peak area of IS compound; ND: not detected.

Table 7. Sensory evaluation analysis of ginger flavored beverages.

Samples	Aroma of Ginger Flavored Beverages (GFB)				Taste of GFBs		
	Fruity	Floral	Gingery	Cooked	Piquant	Sweet	Sour
G1	43.23 ± 2.01 ^a	28.40 ± 4.73 ^a	85.36 ± 3.44 ^b	27.68 ± 4.55 ^a	90.60 ± 2.35 ^b	91.29 ± 0.87 ^a	71.83 ± 3.71 ^a
G2	37.74 ± 2.11 ^b	27.20 ± 7.37 ^a	72.91 ± 4.31 ^a	32.93 ± 4.39 ^b	89.24 ± 1.79 ^b	91.25 ± 1.02 ^a	69.54 ± 3.2 ^a
G3	35.75 ± 2.95 ^b	30.75 ± 5.19 ^a	85.70 ± 2.97 ^b	46.24 ± 3.81 ^c	80.71 ± 2.34 ^a	90.90 ± 0.60 ^a	72.00 ± 3.50 ^a
G4	34.89 ± 3.59 ^b	28.88 ± 4.12 ^a	85.39 ± 3.19 ^b	67.01 ± 3.99 ^d	79.36 ± 2.27 ^a	91.48 ± 0.69 ^a	70.91 ± 3.57 ^a

Mean scores (listed in ascending order) for each attribute within a column with different letters (a, b, c) are significantly different ($p \leq 0.05$) using oneway ANOVA comparison test ($n = 24$; 8 panelists with

3 replication). G1, G2, G3, G4 denotes ginger flavor beverages, prepared without sterilization and sterilization with Ultrahigh-temperature (UHT), atmospheric pressure (AP), and high-pressure (HP) sterilization, respectively. Adapted from [98].

9. Other Ginger Species: Shell Ginger (*Alpinia zerumbet*)

The genus *Alpinia zerumbet* (Pers.) B.L. Burtt & R.M. Sm. (Figure 2) is a perennial plant growing widely in the subtropical and tropical regions including India, Malaysia, China, and Japan as well as Australia and the Pacific Islands [116–118]. It is overwhelmed with phytochemicals including dihydro-5,6-dehydrokawain (DDK), 5,6-dehydrokawain (DK), dihydroflavokawain B, non-kavalactones, methyltriacetolactone, 12-Labdaiene-15,16-dial (labdadiene), among others, thus is used in managing ailments in the above-mentioned countries [116,119,120]. It is speculated that *A. zerumbet* contributes to extending the longevity of Okinawans (indigenes of Okinawa, Japan) [116]. This claim is largely attributed to the unique dihydro-5,6-dehydrokawain (DDK), 5,6-dehydrokawain (DK) as well as phenols, phenolic acids, essential oils, and fatty acids quantified in different parts of the plant (Figure 2) which enhance antioxidant and other biological activities [116,121]. A recent study revealed that *A. zerumbet* leaf extract significantly ($p < 0.001$) extended the mean lifespan of the modeled organism (*Caenorhabditis elegans*) by 22.6% compared to resveratrol, a positive control. Further analysis showed that the extract significantly enhanced the survival rate compared to quercetin under thermal and oxidative stressed states. The potent antioxidant activities and its participation in upregulating superoxide dismutase 3 (SOD-3) and heat-shock protein (HSP-16.2) accredited with the longevity-extending effect [122]. Methanolic leaf extract of *A. zerumbet* exhibited potent antioxidant activity in various assays, namely 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH, 23.54 ± 1.78 (IC₅₀ $\mu\text{g/mL}$), ferric reducing/antioxidant power (FRAP, 13.97 ± 0.43 mM FeSO₄ equivalent/mg extract), 2,20-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS, 5.52 ± 0.34 IC₅₀ $\mu\text{g/mL}$) compared to standards (ascorbic acid, trolox, quercetin) [123]. In vitro and in vivo studies revealed that *A. zerumbet* extracts reduced levels of malondialdehyde (MDA) while concomitantly upregulating SOD, and catalase (CAT) activities [120]. DK and DDK isolated from *A. zerumbet* enhanced alkaline phosphatase activity, matrix mineralization in MC3T3-E1 cells and the expression of runt-related transcription factor 2 (RUNX2) and osterix. Surprisingly, DK exerted larger effects compared to DDK [124]. In addition, there have been reports of Sirtuins (Sirtuin 1 (SIRT1) and Sirtuin 2 (SIRT2)) slowing the ageing process [125–127] thus overexpression of these genes elicited by *A. zerumbet* extracts may extend lifespan [116]. Among the Okinawans, *A. zerumbet* is a common feature of the traditional cuisine as a vegetable and a spice. It is also used to make tea, ice-cream and other beverages as well as processed into foodstuff condiment and candies [116,128]. Moreover, over 30 volatile compounds are identified in essential oils from *A. zerumbet* leaves, including sabinene, limonene, β -phellandrene, 1,8-cineole, γ -terpinene, camphor, linalool, and borneol [129]. With its natural flavor and unique health properties, *A. zerumbet* could open up a new market in the ginger beer industry.

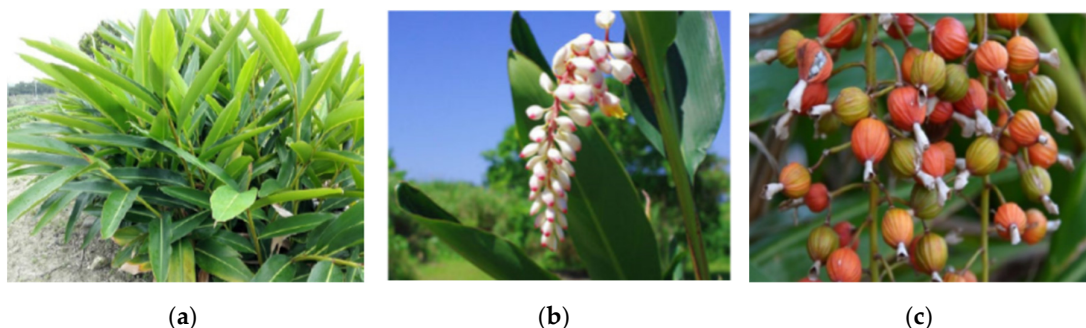


Figure 2. Photos of *Alpinia zerumbet* plant (a), flower (b) and fruits (c). Adapted from [116].

10. Study Limitations

In vitro (Caco-2 cells) and in vivo (animal studies) are efficient methods of assessing the efficacy of bioactive ingredients extracted from plants (i.e., ginger). The merits of these methods include: 1. low cost; 2. less time require to conduct an experiment; 3. rapid physiological response; 4. easy identification of biomarkers; etc. On the other hand, these methods are labor intensive and results obtained do not usually reflect the physiological and metabolic response of the human system. For instance, the biological and pharmacological effects of ginger extracts are largely reported based on in vitro and in vivo (animal studies, i.e., rats) studies which may not represent the efficacy it has on humans and their diseases. Dias et al. emphasized the relevance of in vitro and in vivo studies to understanding the effects of bioactive compounds, but also caution on the interpretation of such results, especially when human studies are not extensively involved. They further recommended the combination of in vitro, animal and human studies as an effective method of elucidating the effects of active compounds on test subjects [130]. Similar concerns were raised by Roberts and colleagues where they indicated that in vitro methods such as microtitre plate assays and flow cells do not accurately represent in vivo conditions [131]. Therefore, extensive human trial is needed to further confirm the health benefits that the consumer may derive consuming ginger beer.

11. Conclusions

Ginger is a widely used food spice, famous for its distinctive aromatic odor. Traditionally, it is acknowledged as a medicinal plant with various biological and pharmacological activities including antioxidant, anti-inflammatory, antimicrobial and analgesic activities and is used to manage ailments such as cold, headaches, toothaches etc. Its use as a medicinal plant is corroborated by extensive scientific studies which show that it has, in addition, anticancer, antidiabetic and anti-hypercholesteremic activities. The medicinal properties of ginger are directly linked to its phytoconstituents which include shogaols, zingerones, gingerols, gingerenones, etc. It is also rich in nutritive components, i.e., carbohydrates, proteins, vitamins and minerals. Following the ever-increasing consumer preference for healthy drinks and beverages, the market for ginger beer has blossomed. To further satisfy consumers' demand, products with fewer chemical additives and the use of natural ginger extract to produce ginger beer, as described in this text, is more desirable. Moreover, the use of natural ginger extract would enrich resulting beer with its bioactive and nutritional constituents which consequently could promote the general wellbeing of consumers.

Author Contributions: Conceptualization, C.N., J.A.E., P.A. and O.N.K.; Writing—Original Draft Preparation, C.N., J.A.E.; Writing—Review & Editing, P.A. and O.N.K. All authors have read and agreed to the published version of the manuscript.

Funding: No funding received.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Mahomoodally, M.F.; Aumeeruddy, M.Z.; Rengasamy, K.R.R.; Roshan, S.; Hammad, S.; Pandohee, J.; Hu, X.; Zengin, G. Ginger and its active compounds in cancer therapy: From folk uses to nano-therapeutic applications. *Semin. Cancer Biol.* **2019**, in press, doi:10.1016/j.semcancer.2019.08.009.
2. Bag, B.B. Ginger processing in India (*Zingiber officinale*): A review. *Int. J. Curr. Microbiol. App. Sci.* **2018**, *7*, 1639–1651, doi:10.20546/ijcmas.2018.704.185.
3. Li, H.; Liu, Y.; Luo, D.; Ma, Y.; Zhang, J.; Li, M.; Yao, L.; Shi, X.; Liu, X.; Yang, K. Ginger for health care: An overview of systematic reviews. *Complement. Ther. Med.* **2019**, *45*, 114–123, doi:10.1016/j.ctim.2019.06.002.
4. Srinivasan, K. Ginger rhizomes (*Zingiber officinale*): A spice with multiple health beneficial potentials. *PharmaNutrition* **2017**, *5*, 18–28, doi:10.1016/j.phanu.2017.01.001.
5. Madden, D. Ginger beer: A traditional fermented lowalcohol drink. *Eur. J. Sci. Teach.* **2008**, *8*, 29–33.
6. Bellut, K.; Arendt, E.K. Chance and challenge: Non-saccharomyces yeasts in nonalcoholic and low alcohol beer brewing—A review. *J. Am. Soc. Brew. Chem.* **2019**, *77*, 77–91, doi:10.1080/03610470.2019.1569452.

7. Adadi, P.; Kovaleva, E.; Glukhareva, T.; Shatunova, S.; Petrov, A. Production and analysis of non-traditional beer supplemented with sea buckthorn. *Agron. Res.* **2017**, *15*, 1831–1845, doi:10.15159/AR.17.060.
8. Ducruet, J.; Rébénacque, P.; Diserens, S.; Kosińska-Cagnazzo, A.; Héritier, I.; Andlauer, W. Amber ale beer enriched with goji berries—The effect on bioactive compound content and sensorial properties. *Food Chem.* **2017**, *226*, 109–118, doi:10.1016/j.foodchem.2017.01.047.
9. Kawa-Rygielska, J.; Adamenko, K.; Kucharska, A.Z.; Prorok, P.; Piórecki, N. Physicochemical and antioxidative properties of Cornelian cherry beer. *Food Chem.* **2019**, *281*, 147–153, doi:10.1016/j.foodchem.2018.12.093.
10. Dookeran, M.M.; Baccus-Taylor, G.S.; Akingbala, J.O. Laboratory manufacture and comparison of ginger (*Zingiber officinale* Roscoe) beer quality. *J. Food Agric. Environ.* **2004**, *2*, 29–33, doi:10.1234/4.2004.248.
11. Tozetto, L.M.; Nascimento, R.F.d.; Oliveira, M.H.d.; Van Beik, J.; Canteri, M.H.G. Production and physicochemical characterization of craft beer with ginger (*Zingiber officinale*). *Food Sci. Technol.* **2019**, *39*, 962–970, doi:10.1590/fst.16518.
12. Zion Market Research. Ginger Beer Market: Global Industry Perspective, Comprehensive Analysis, and forecast, 2018–2025. 2019. Available online: <https://www.zionmarketresearch.com/report/ginger-beer-market> (accessed on 30 August 2020).
13. Gaikwad, K.K.; Singh, S.; Shakyia, B. Studies on the development and shelf life of low calorie herbal aonla-ginger RTS beverage by using artificial sweeteners. *J. Food Process. Technol.* **2013**, *4*, 2.
14. OpenPR. Ginger Beer Market to Witness Huge Growth by 2025. Affinity Beverages, Fever-Tree, Q Mixers, Goslings Rum. 2019. Available online: <https://www.openpr.com/news/1829148/ginger-beer-market-to-witness-huge-growth-by-2025-affinity> (assessed on 30 August 2020).
15. Singh, A. Nutritional benefits and pharmacological effects of ginger: An overview. *Indian J. Basic Appl. Med. Res.* **2015**, *4*, 377–383.
16. Langner, E.; Greifenberg, S.; Gruenwald, J. Ginger: History and use. *Adv. Ther.* **1998**, *15*, 25–44.
17. Al-Achi, A. A current look at ginger use. *US Pharm.* **2001**, *26*, HS13.
18. Ajayi, O.B.; Akomolafe, S.F.; Akinyemi, F.T. Food value of two varieties of ginger (*Zingiber officinale*) commonly consumed in Nigeria. *ISRN Nutr.* **2013**, *2013*, 359727, doi:10.5402/2013/359727.
19. Bhatt, N.; Waly, M.I.; Essa, M.M.; Ali, A. Ginger: A functional herb. In *Food as Medicine*; Nova Science Publishers, Inc.:Hauppauge, NY, USA, 2013; pp 51–72.
20. Latona, D.; Oyeleke, G.; Olayiwola, O. Chemical analysis of ginger root. *J. Appl. Chem.* **2012**, *1*, 47–49.
21. Yeh, H.-Y.; Chuang, C.-H.; Chen, H.-C.; Wan, C.-J.; Chen, T.-L.; Lin, L.-Y. Bioactive components analysis of two various gingers (*Zingiber officinale* Roscoe) and antioxidant effect of ginger extracts. *LWT-Food Sci. Technol.* **2014**, *55*, 329–334, doi:10.1016/j.lwt.2013.08.003.
22. Onimawo, I.A.; Esekheigbe, A.; Okoh, J.E. Determination of Proximate and Mineral Composition of Three Traditional Spices. *ASNH* **2019**, *3*, 111–114, doi:10.1016/j.lwt.2013.08.003.
23. Chrubasik, S.; Pittler, M.H.; Roufogalis, B.D. Zingiberis rhizoma: A comprehensive review on the ginger effect and efficacy profiles. *Phytomedicine* **2005**, *12*, 684–701, doi:10.1016/j.phymed.2004.07.009.
24. Baliga, M.S.; Haniadka, R.; Pereira, M.M.; Thilakchand, K.R.; Rao, S.; Arora, R. Radioprotective effects of *Zingiber officinale* Roscoe (ginger): Past, present and future. *Food Funct.* **2012**, *3*, 714–723, doi:10.1039/c2fo10225k.
25. Tohma, H.; Gülçin, İ.; Bursal, E.; Gören, A.C.; Alwasel, S.H.; Köksal, E. Antioxidant activity and phenolic compounds of ginger (*Zingiber officinale* Rosc.) determined by HPLC-MS/MS. *J. Food Meas. Charact.* **2016**, *11*, 556–566, doi:10.1007/s11694-016-9423-z.
26. McKay, D. Can hibiscus tea lower blood pressure. *Agro. Food Ind. Hi-Tech.* **2009**, *20*, 40–42.
27. Ghasemzadeh, A.; Jaafar, H.Z.; Rahmat, A. Synthesis of phenolics and flavonoids in ginger (*Zingiber officinale* Roscoe) and their effects on photosynthesis rate. *Int. J. Mol. Sci.* **2010**, *11*, 4539–4555, doi:10.3390/ijms11114539.
28. Mošovská, S.; Nováková, D.; Kaliňák, M. Antioxidant activity of ginger extract and identification of its active components. *Acta Chim. Slov.* **2015**, *8*, 115–119, doi:10.1515/acs-2015-0020.
29. Ali, A.M.A.; El-Nour, M.E.M.; Yagi, S.M. Total phenolic and flavonoid contents and antioxidant activity of ginger (*Zingiber officinale* Rosc.) rhizome, callus and callus treated with some elicitors. *J. Genet. Eng. Biotechnol.* **2018**, *16*, 677–682, doi:10.1016/j.jgeb.2018.03.003.

30. Tanweer, S.; Mehmood, T.; Zainab, S.; Ahmad, Z.; Shehzad, A. Comparison and HPLC quantification of antioxidant profiling of ginger rhizome, leaves and flower extracts. *Clin. Phytosci.* **2020**, *6*, 1–12, doi:10.1186/s40816-020-00158-z.
31. El-Ghorab, A.H.; Nauman, M.; Anjum, F.M.; Hussain, S.; Nadeem, M. A comparative study on chemical composition and antioxidant activity of ginger (*Zingiber officinale*) and cumin (*Cuminum cyminum*). *J. Agric. Food Chem.* **2010**, *58*, 8231–8237, doi:10.1021/jf101202x.
32. Osabor, V.; Bassey, F.; Umoh, U. Phytochemical screening and quantitative evaluation of nutritional values of *Zingiber officinale* (Ginger). *Chem. Sci. Int. J.* **2015**, 1–6, doi:10.9734/ACSj/2015/16915.
33. Ghasemzadeh, A.; Jaafar, H.Z.; Rahmat, A. Antioxidant activities, total phenolics and flavonoids content in two varieties of Malaysia young ginger (*Zingiber officinale* Roscoe). *Molecules* **2010**, *15*, 4324–4333, doi:10.3390/molecules15064324.
34. Ogbuwu, I.; Jiwuba, P.; Ezeokeke, C.; Uchegbu, M.; Okoli, I.; Iloeje, M. Evaluation of phytochemical and nutritional composition of ginger rhizome powder. *Int. J. Agric. Rural Develop.* **2014**, *17*, 1663–1670.
35. Cao, S.-Y.; Li, Y.; Meng, X.; Zhao, C.-N.; Li, S.; Gan, R.-Y.; Li, H.-B. Dietary natural products and lung cancer: Effects and mechanisms of action. *J. Funct. Foods* **2019**, *52*, 316–331, doi:10.1016/j.jff.2018.11.004.
36. Dugasani, S.; Pichika, M.R.; Nadarajah, V.D.; Balijepalli, M.K.; Tandra, S.; Korlakunta, J.N. Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol. *J. Ethnopharmacol.* **2010**, *127*, 515–520, doi:10.1016/j.jep.2009.10.004.
37. Rahmani, A.H.; Al Shabrmi, F.M.; Aly, S.M. Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities. *Int. J. Physiol. Pathophysiol. Pharmacol.* **2014**, *6*, 125–136.
38. Aeschbach, R.; Loliger, J.; Scott, B.C.; Murcia, A.; Butler, J.; Halliwell, B.; Aruoma, O.I. Antioxidant actions of thymol, carvacrol, 6-gingerol, zingerone and hydroxytyrosol. *Food Chem. Toxicol.* **1994**, *32*, 31–36, doi:10.1016/0278-6915(84)90033-4.
39. Chang, W.S.; Chang, Y.H.; Lu, F.J.; Chiang, H.C. Inhibitory effects of phenolics on xanthine oxidase. *Anticancer Res.* **1994**, *14*, 501–506.
40. Shukla, Y.; Singh, M. Cancer preventive properties of ginger: A brief review. *Food Chem. Toxicol.* **2007**, *45*, 683–690, doi:10.1016/j.fct.2006.11.002.
41. Bak, M.J.; Ok, S.; Jun, M.; Jeong, W.S. 6-shogaol-rich extract from ginger up-regulates the antioxidant defense systems in cells and mice. *Molecules* **2012**, *17*, 8037–8055, doi:10.3390/molecules17078037.
42. Abd El-Kaream, S.A. Biochemical and biophysical study of chemopreventive and chemotherapeutic anti-tumor potential of some Egyptian plant extracts. *Biochem. Biophys. Rep.* **2019**, *18*, 100637, doi:10.1016/j.bbrep.2019.100637.
43. Habib, S.H.; Makpol, S.; Abdul Hamid, N.A.; Das, S.; Ngah, W.Z.; Yusof, Y.A. Ginger extract (*Zingiber officinale*) has anti-cancer and anti-inflammatory effects on ethionine-induced hepatoma rats. *Clinics* **2008**, *63*, 807–813, doi:10.1590/s1807-59322008000600017.
44. Manju, V.; Nalini, N. Chemopreventive efficacy of ginger, a naturally occurring anticarcinogen during the initiation, post-initiation stages of 1,2 dimethylhydrazine-induced colon cancer. *Clin. Chim. Acta* **2005**, *358*, 60–67, doi:10.1016/j.cccn.2005.02.018.
45. Ramakrishnan, R. Anticancer properties of *Zingiber officinale*—Ginger: A review. *Int. J. Med. Pharm. Sci.* **2013**, *3*, 11–20.
46. Rhode, J.; Fogoros, S.; Zick, S.; Wahl, H.; Griffith, K.A.; Huang, J.; Liu, J.R. Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells. *BMC Complement. Altern. Med.* **2007**, *7*, 44, doi:10.1186/1472-6882-7-44.
47. Wang, X.; Zhu, S.; Pei, Z.; Drozda, M.; Stavrovskaya, I.G.; Del Signore, S.J.; Cormier, K.; Shimony, E.M.; Wang, H.; Ferrante, R.J.; et al. Inhibitors of cytochrome c release with therapeutic potential for Huntington's disease. *J. Neurosci.* **2008**, *28*, 9473–9485, doi:10.1523/JNEUROSCI.1867-08.2008.
48. Lee, H.S.; Seo, E.Y.; Kang, N.E.; Kim, W.K. [6]-Gingerol inhibits metastasis of MDA-MB-231 human breast cancer cells. *J. Nutr. Biochem.* **2008**, *19*, 313–319, doi:10.1016/j.jnutbio.2007.05.008.
49. Jeong, C.H.; Bode, A.M.; Pugliese, A.; Cho, Y.Y.; Kim, H.G.; Shim, J.H.; Jeon, Y.J.; Li, H.; Jiang, H.; Dong, Z. [6]-Gingerol suppresses colon cancer growth by targeting leukotriene A4 hydrolase. *Cancer Res.* **2009**, *69*, 5584–5591, doi:10.1158/0008-5472.CAN-09-0491.

50. Kim, S.O.; Chun, K.S.; Kundu, J.K.; Surh, Y.J. Inhibitory effects of [6]-gingerol on PMA-induced COX-2 expression and activation of NF-kappaB and p38 MAPK in mouse skin. *Biofactors* **2004**, *21*, 27–31, doi:10.1002/biof.552210107.
51. Yodkeeree, S.; Sung, B.; Limtrakul, P.; Aggarwal, B.B. Zerumbone enhances TRAIL-induced apoptosis through the induction of death receptors in human colon cancer cells: Evidence for an essential role of reactive oxygen species. *Cancer Res.* **2009**, *69*, 6581–6589, doi:10.1158/0008-5472.CAN-09-1161.
52. Sung, M.-H.; Salvatore, L.; De Lorenzi, R.; Indrawan, A.; Pasparakis, M.; Hager, G.L.; Bianchi, M.E.; Agresti, A. Sustained oscillations of NF-κB produce distinct genome scanning and gene expression profiles. *PLoS ONE* **2009**, *4*, e7163.
53. Huang, W.C.; Hung, M.C. Induction of Akt activity by chemotherapy confers acquired resistance. *J. Formos Med. Assoc.* **2009**, *108*, 180–194, doi:10.1016/S0929-6646(09)60051-6.
54. Ling, H.; Yang, H.; Tan, S.H.; Chui, W.K.; Chew, E.H. 6-Shogaol, an active constituent of ginger, inhibits breast cancer cell invasion by reducing matrix metalloproteinase-9 expression via blockade of nuclear factor-kappaB activation. *Br. J. Pharmacol.* **2010**, *161*, 1763–1777, doi:10.1111/j.1476-5381.2010.00991.x.
55. Peng, F.; Tao, Q.; Wu, X.; Dou, H.; Spencer, S.; Mang, C.; Xu, L.; Sun, L.; Zhao, Y.; Li, H.; et al. Cytotoxic, cytoprotective and antioxidant effects of isolated phenolic compounds from fresh ginger. *Fitoterapia* **2012**, *83*, 568–585, doi:10.1016/j.fitote.2011.12.028.
56. Liu, Y.; Whelan, R.J.; Pattnaik, B.R.; Ludwig, K.; Subudhi, E.; Rowland, H.; Claussen, N.; Zucker, N.; Uppal, S.; Kushner, D.M.; et al. Terpenoids from *Zingiber officinale* (Ginger) induce apoptosis in endometrial cancer cells through the activation of p53. *PLoS ONE* **2012**, *7*, e53178, doi:10.1371/journal.pone.0053178.
57. Zhu, Y.; Warin, R.F.; Soroka, D.N.; Chen, H.; Sang, S. Metabolites of ginger component [6]-shogaol remain bioactive in cancer cells and have low toxicity in normal cells: Chemical synthesis and biological evaluation. *PLoS ONE* **2013**, *8*, e54677, doi:10.1371/journal.pone.0054677.
58. Kanwugu, O.N.; Helegbe, G.K.; Aryee, P.A.; Akontatiba, N.A.; Ankrah, J.; Anabire, N.G.; Anaba, F.; Ahenkora, B. A comparative assessment of the glucose monitor (SD Codefree) and auto analyzer (BT-3000) in measuring blood glucose concentration among diabetic patients. *BMC Res. Notes* **2017**, *10*, 453.
59. Jafri, S.A.; Abass, S.; Qasim, M. Hypoglycemic effect of ginger (*Zingiber officinale*) in alloxan induced diabetic rats (*Rattus norvegicus*). *Pak. Vet. J.* **2011**, *31*, 160–162.
60. American Diabetes Association (ADA). Diagnosis and classification of diabetes mellitus. *Diabetes Care* **2014**, *37*, S81–S90, doi:10.2337/dc14-S081.
61. Li, Y.; Tran, V.H.; Duke, C.C.; Roufogalis, B.D. Preventive and protective properties of *Zingiber officinale* (Ginger) in diabetes mellitus, diabetic complications, and associated lipid and other metabolic disorders: A brief review. *Evid Based Complement. Altern. Med.* **2012**, *2012*, 516870, doi:10.1155/2012/516870.
62. Sharma, M.; Shukla, S. Hypoglycaemic effect of ginger. *J. Res. Indian Med. Yoga Homeopat.* **1977**, *12*, 127–130.
63. Oboh, G.; Akinyemi, A.J.; Ademiluyi, A.O.; Adefegha, S.A. Inhibitory effects of aqueous extract of two varieties of ginger on some key enzymes linked to type-2 diabetes in vitro. *J. Food. Nutr. Res.* **2010**, *49*, 14–20.
64. Akhiani, S.P.; Vishwakarma, S.L.; Goyal, R.K. Anti-diabetic activity of *Zingiber officinale* in streptozotocin-induced type I diabetic rats. *J. Pharm. Pharmacol.* **2004**, *56*, 101–105, doi:10.1211/0022357022403.
65. Bhandari, U.; Kanojia, R.; Pillai, K.K. Effect of ethanolic extract of *Zingiber officinale* on dyslipidaemia in diabetic rats. *J. Ethnopharmacol.* **2005**, *97*, 227–230, doi:10.1016/j.jep.2004.11.011.
66. Chukwudike, A.M.M.; Mercy, B.O. Dose-dependent antidiabetic and antiobesity potentials of aqueous extract of *Zingiber officinale* Linn (Ginger) rhizomes in experimental diabetic rats: Need for precaution? *EC Nutr.* **2019**, *14*, 468–473.
67. Salim, K.S. The Effect of oral administration of green tea and ginger extracts on blood glucose in diabetic rats. *Int. J. Drug Deliv. Technol.* **2019**, *9*, 41–46, doi:10.25258/ijddt.v9i3.17.
68. Hajimoosayi, F.; Jahanian Sadatmahalleh, S.; Kazemnejad, A.; Pirjani, R. Effect of ginger on the blood glucose level of women with gestational diabetes mellitus (GDM) with impaired glucose tolerance test (GTT): A randomized double-blind placebo-controlled trial. *BMC Complement. Med. Ther* **2020**, *20*, 116, doi:10.1186/s12906-020-02908-5.
69. Rafie, R.; Hosseini, S.A.; Hajiani, E.; Saki Malehi, A.; Mard, S.A. Effect of ginger powder supplementation in patients with non-alcoholic fatty liver disease: A randomized clinical trial. *Clin. Exp. Gastroenterol.* **2020**, *13*, 35–45, doi:10.2147/CEG.S234698.

70. Shidfar, F.; Rajab, A.; Rahideh, T.; Khandouzi, N.; Hosseini, S.; Shidfar, S. The effect of ginger (*Zingiber officinale*) on glycemic markers in patients with type 2 diabetes. *J. Complement. Integr. Med.* **2015**, *12*, 165–170, doi:10.1515/jcim-2014-0021.
71. Abifadel, M.; Varret, M.; Rabes, J.P.; Allard, D.; Ouguerram, K.; Devillers, M.; Cruaud, C.; Benjannet, S.; Wickham, L.; Erlich, D.; et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat. Genet.* **2003**, *34*, 154–156, doi:10.1038/ng1161.
72. Goldstein, J.L. *Familial Hypercholesterolemia*; Parkland Memorial Hospital: Dallas, TX, USA, 1974.
73. ElRokh el, S.M.; Yassin, N.A.; El-Shenawy, S.M.; Ibrahim, B.M. Antihypercholesterolaemic effect of ginger rhizome (*Zingiber officinale*) in rats. *Inflammopharmacology* **2010**, *18*, 309–315, doi:10.1007/s10787-010-0053-5.
74. Bhandari, U.; Sharma, J.N.; Zafar, R. The protective action of ethanolic ginger (*Zingiber officinale*) extract in cholesterol fed rabbits. *J. Ethnopharmacol.* **1998**, *61*, 167–171, doi:10.1016/s0378-8741(98)00026-9.
75. Thomson, M.; Al-Qattan, K.; Al-Sawan, S.; Alnaqeeb, M.; Khan, I.; Ali, M. The use of ginger (*Zingiber officinale* Rosc.) as a potential anti-inflammatory and antithrombotic agent. *Prostaglandins Leukot. Essent. Fatty Acids* **2002**, *67*, 475–478, doi:10.1054/plef.2002.0441.
76. Sharma, J.N.; Srivastava, K.C.; Gan, E.K. Suppressive effects of eugenol and ginger oil on arthritic rats. *Pharmacology* **1994**, *49*, 314–318, doi:10.1159/000139248.
77. Funk, J.L.; Frye, J.B.; Oyarzo, J.N.; Chen, J.; Zhang, H.; Timmermann, B.N. Anti-inflammatory effects of the essential oils of ginger (*Zingiber officinale* Roscoe) in experimental rheumatoid arthritis. *PharmaNutrition* **2016**, *4*, 123–131, doi:10.1016/j.phanu.2016.02.004.
78. Jia, Y.-I.; Zhao, J.-m.; Zhang, L.-h.; Sun, B.-s.; Bao, M.-j.; Li, F.-f.; Shen, J.; Shen, H.; Zhao, Y.; Xie, Q. Analgesic and anti-inflammatory effects of ginger oil. *Chin. Herb. Med.* **2011**, *3*, 150–155, doi:10.3969/j.issn.1674-6384.2011.02.011.
79. Luettig, J.; Rosenthal, R.; Lee, I.M.; Krug, S.M.; Schulzke, J.D. The ginger component 6-shogaol prevents TNF- α -induced barrier loss via inhibition of PI3K/Akt and NF- κ B signaling. *Mol. Nutr. Food Res.* **2016**, *60*, 2576–2586, doi:10.1002/mnfr.201600274.
80. Zhang, G.; Nitteranon, V.; Chan, L.Y.; Parkin, K.L. Glutathione conjugation attenuates biological activities of 6-dehydroshogaol from ginger. *Food Chem.* **2013**, *140*, 1–8, doi:10.1016/j.foodchem.2013.02.073.
81. Mohammadi, F.; Nikzad, H.; Taghizadeh, M.; Taherian, A.; Azami-Tameh, A.; Hosseini, S.M.; Moravveji, A. Protective effect of *Zingiber officinale* extract on rat testis after cyclophosphamide treatment. *Andrologia* **2014**, *46*, 680–686, doi:10.1111/and.12135.
82. Zhang, M.; Viennois, E.; Prasad, M.; Zhang, Y.; Wang, L.; Zhang, Z.; Han, M.K.; Xiao, B.; Xu, C.; Srinivasan, S.; et al. Edible ginger-derived nanoparticles: A novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis-associated cancer. *Biomaterials* **2016**, *101*, 321–340, doi:10.1016/j.biomaterials.2016.06.018.
83. Hsiang, C.-Y.; Lo, H.-Y.; Huang, H.-C.; Li, C.-C.; Wu, S.-L.; Ho, T.-Y. Ginger extract and zingerone ameliorated trinitrobenzene sulphonic acid-induced colitis in mice via modulation of nuclear factor- κ B activity and interleukin-1 β signalling pathway. *Food Chem.* **2013**, *136*, 170–177, doi:10.1016/j.foodchem.2012.07.124.
84. Kaneko, M.; Kishimoto, Y.; Suzuki, R.; Kawai, Y.; Tateya, I.; Hirano, S. Protective effect of astaxanthin on vocal fold injury and inflammation due to vocal loading: A clinical trial. *J. Voice* **2017**, *31*, 352–358, doi:10.1016/j.jvoice.2016.06.017.
85. United States Food and Drug Administration. *Essential Oils, Oleoresins (Solvent Free), and Natural Extractives Including Distillates*; Code of Federal Regulations; U.S. Government Publishing Office: Washington, DC, USA, 2003.
86. Wilkinson, J.M. Effect of ginger tea on the fetal development of Sprague-Dawley rats. *Reprod. Toxicol.* **2000**, *14*, 507–512, doi:10.1016/s0890-6238(00)00106-4.
87. Weidner, M.S.; Sigwart, K. Investigation of the teratogenic potential of a *Zingiber officinale* extract in the rat. *Reprod. Toxicol.* **2000**, *15*, 75–80, doi:10.1016/s0890-6238(00)00116-7.
88. Rong, X.; Peng, G.; Suzuki, T.; Yang, Q.; Yamahara, J.; Li, Y. A 35-day gavage safety assessment of ginger in rats. *Regul. Toxicol. Pharmacol.* **2009**, *54*, 118–123, doi:10.1016/j.yrtph.2009.03.002.
89. Idang, E.O.; Yemitan, O.K.; Mbagwu, H.O.; Udom, G.J.; Ogbuagu, E.O.; Udobang, J.A. Toxicological assessment of *Zingiber officinale* Roscoe (Ginger) root oil extracts in Albino rats. *Toxicol. Digest* **2019**, *4*, 108–119.
90. Jeena, K.; Liju, V.B.; Kuttan, R. A preliminary 13-week oral toxicity study of ginger oil in male and female Wistar rats. *Int. J. Toxicol.* **2011**, *30*, 662–670, doi:10.1177/1091581811419023.

91. Nwaopara, A.O.; Odike, M.A.C.; Inegbenebor, U.; Adoye, M.I. The Combined effects of excessive consumption of ginger, clove, red pepper and black pepper on the histology of the liver. *Pak. J. Nutr.* **2007**, *6*, 524–527, doi:10.3923/pjn.2007.524.527.
92. Dookeran, M.M. Investigation into the Laboratory-Scale Production of Ginger (*Zingiber officinale* Roscoe) Beer by Natural and Controlled Fermentation. Master's Thesis, University of the West Indies, Trinidad and Tobago, 2003.
93. Adadi, P.; Kovaleva, E.G.; Glukhareva, T.V.; Barakova, N.V. Production and investigations of antioxidant rich beverage: Utilizing monascus purpureus IHEM LY2014-0696 and various malts. *Agron. Res.* **2018**, *16*, 1312–1321, doi:10.15159/AR.18.028.
94. Adadi, P.; Kovaleva, E.G.; Glukhareva, T.V.; Shatunova, S.A. Biotechnological production of non-traditional beer. *AIP Conf. Proc.* **2017**, *1886*, 1–13, doi:10.1063/1.5002995.
95. Adadi, P.; Kanwugu, O.N. Potential application of tetrapleura tetraptera and hibiscus sabdariffa (malvaceae) in designing highly flavoured and bioactive pito with functional properties. *Beverages* **2020**, *6*, 1–32, doi:10.3390/beverages6020022.
96. Nsengumuremyi, D.; Adadi, P.; Ukolova, M.V.; Barakova, N.V. Effects of ultradisperse humic sapropel suspension on microbial growth and fermentation parameters of barley distillate. *Fermentation* **2019**, *5*, 24, doi:10.3390/fermentation5010024.
97. Chen, Y.-C.; Shen, H.-J.; Zhang, S.-J. Development of ginger beer. *Liquor-Making Sci. Technol.* **1999**, *6*. http://en.cnki.com.cn/Article_en/CJFDTotol-NJKJ199906028.htm?fbclid=IwAR2P8K5cxMbPUxQ-h5kaHXbuu2SQosanxgu4qJRpgWzVQa7-1wxoJbPHjg (accessed on 30 August 2020).
98. Liu, F.; Song, S.; Zhang, X.; Tan, C.; Karangwa, E. Effect of sterilization methods on ginger flavor beverage assessed by partial least squares regression of descriptive sensory analysis and gas chromatography–mass spectrometry. *Eur. Food Res. Technol.* **2013**, *238*, 247–257, doi:10.1007/s00217-013-2093-8.
99. AECOM Services Pty Ltd. *Development of a Ginger Product to Add Value to the Fijian Ginger Industry*; AECOM Services: Adelaide, SA, Australia, 2016.
100. Yang, Z.-N.; Yang, W.; Peng, Q.; He, Q.; Feng, Y.; Luo, S.; Yu, Z. Volatile phytochemical composition of rhizome of ginger after extraction by headspace solid-phase microextraction, petrol ether extraction and steam distillation extraction. *Bangladesh J. Pharmacol.* **2009**, *4*, 136–143, doi:10.3329/bjp.v4i2.3232.
101. Gong, F.; Fung, Y.-S.; Liang, Y.-Z. Determination of volatile components in ginger using gas chromatography–mass spectrometry with resolution improved by data processing techniques. *J. Agric. Food Chem.* **2004**, *52*, 6378–6383.
102. Höferl, M.; Stoilova, I.; Wanner, J.; Schmidt, E.; Jirovets, L.; Trifonova, D.; Stanchev, V.; Krastanov, A. Composition and Comprehensive Antioxidant Activity of Ginger (*Zingiber officinale*) Essential Oil from Ecuador. *Nat. Prod. Commun.* **2015**, *10*, doi:10.1177/1934578x1501000672.
103. Ding, S.H.; An, K.J.; Zhao, C.P.; Li, Y.; Guo, Y.H.; Wang, Z.F. Effect of drying methods on volatiles of Chinese ginger (*Zingiber officinale* Roscoe). *Food Bioprod. Process.* **2012**, *90*, 515–524, doi:10.1016/j.fbp.2011.10.003.
104. Saerens, S.M.; Delvaux, F.R.; Verstrepen, K.J.; Thevelein, J.M. Production and biological function of volatile esters in *Saccharomyces cerevisiae*. *Microb. Biotechnol.* **2010**, *3*, 165–177, doi:10.1111/j.1751-7915.2009.00106.x.
105. Verstrepen, K.J.; Derdelinckx, G.; Dufour, J.P.; Winderickx, J.; Thevelein, J.M.; Pretorius, I.S.; Delvaux, F.R. Flavor-active esters: Adding fruitiness to beer. *J. Biosci. Bioeng.* **2003**, *96*, 110–118, doi:10.1016/S1389-1723(03)90112-5.
106. Blanco, C.A.; Andres-Iglesias, C.; Montero, O. Low-alcohol beers: Flavor compounds, defects, and improvement strategies. *Crit. Rev. Food Sci. Nutr.* **2016**, *56*, 1379–1388, doi:10.1080/10408398.2012.733979.
107. Pinho, O.; Ferreira, I.M.; Santos, L.H. Method optimization by solid-phase micro-extraction in combination with gas chromatography-mass spectrometry for analysis of beer volatile fraction. *J. Chrom. A* **2006**, *1121*, 145–153, doi:10.1016/j.chroma.2006.04.013.
108. Eyres, G.; Dufour, J.P. Hop Essential Oil: Analysis, chemical composition and odor characteristics. In *Beer in Health and Disease Prevention*, Elsevier: Cambridge, MA, USA, 2008; pp. 239–254.
109. Eyres, G.T.; Marriott, P.J.; Dufour, J.P. Comparison of odor-active compounds in the spicy fraction of hop (*Humulus lupulus* L.) essential oil from four different varieties. *J. Agric. Food Chem.* **2007**, *55*, 6252–6261, doi:10.1021/jf070739t.

110. Rettberg, N.; Biendl, M.; Garbe, L.-A. Hop aroma and hoppy beer flavor: Chemical backgrounds and analytical tools—A review. *J. Am. Soc. Brew. Chem.* **2018**, *76*, 1–20, doi:10.1080/03610470.2017.1402574.
111. Richter, T.M.; Silcock, P.; Algarra, A.; Eyres, G.T.; Capozzi, V.; Bremer, P.J.; Biasioli, F. Evaluation of PTR-ToF-MS as a tool to track the behavior of hop-derived compounds during the fermentation of beer. *Food Res. Int.* **2018**, *111*, 582–589, doi:10.1016/j.foodres.2018.05.056.
112. Richter, T.M.; Eyres, G.T.; Silcock, P.; Bremer, P.J. Comparison of four extraction methods for analysis of volatile hop-derived aroma compounds in beer. *J. Sep. Sci.* **2017**, *40*, 4366–4376, doi:10.1002/jssc.201700676.
113. Adadi, P.; Barakova, N.V.; Krivoschapkina, E.F. Scientific approaches to improving artisan methods of producing local food condiments in Ghana. *Food Control.* **2019**, *106*, 106682, doi:10.1016/j.foodcont.2019.06.008.
114. Saison, D.; De Schutter, D.P.; Delvaux, F.; Delvaux, F.R. Optimisation of a complete method for the analysis of volatiles involved in the flavor stability of beer by solid-phase microextraction in combination with gas chromatography and mass spectrometry. *J. Chromatogr. A* **2008**, *1190*, 342–349, doi:10.1016/j.chroma.2008.03.015.
115. Halimah, H.; Maddeppungeng, N.R. *Instant Ginger Beer the Traditional Health Drinks from Buginese-Makassar*; Trans Tech Publications Ltd.: Kapellweg, Switzerland, 2019; Volume 967 MSF, pp. 107–112.
116. Teschke, R.; Xuan, T.D. A contributory role of shell ginger (*Alpinia zerumbet*) for human longevity in Okinawa, Japan? *Nutrients* **2018**, *10*, 166, doi:10.3390/nu10020166.
117. Ma, X.-N.; Xie, C.-L.; Miao, Z.; Yang, Q.; Yang, X.-W. An overview of chemical constituents from *Alpinia* species in the last six decades. *RSC Adv.* **2017**, *7*, 14114–14144, doi:10.1039/C6RA27830B.
118. Tao, L.; Hu, H.S.; Shen, X.C. Endothelium-dependent vasodilatation effects of the essential oil from *Fructus alpiniae zerumbet* (EOFAZ) on rat thoracic aortic rings in vitro. *Phytomedicine* **2013**, *20*, 387–393, doi:10.1016/j.phymed.2012.12.014.
119. Tawata, S.; Fukuta, M.; Xuan, T.D.; Deba, F. Total utilization of tropical plants *Leucaena leucocephala* and *Alpinia zerumbet*. *J. Pestic. Sci* **2008**, *33*, 40–43, doi:10.1584/jpestics.R07-10.
120. Zahra, M.H.; Salem, T.A.; El-Aarag, B.; Yosri, N.; El-Ghlban, S.; Zaki, K.; Marei, A.H.; El-Wahed, A.; Saeed, A.; Khatib, A. *Alpinia zerumbet* (Pers.): Food and medicinal plant with potential in vitro and in vivo anti-cancer activities. *Molecules* **2019**, *24*, 2495, doi:10.3390/molecules24132495.
121. Tawata, S.; Taira, S.; Kobamoto, N.; Ishihara, M.; Toyama, S. Syntheses and biological activities of dihydro-5, 6-dehydrokawain derivatives. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 1643–1645, doi:10.1271/bbb.60.1643.
122. Upadhyay, A.; Chompoo, J.; Taira, N.; Fukuta, M.; Tawata, S. Significant longevity-extending effects of *Alpinia zerumbet* leaf extract on the life span of *Caenorhabditis elegans*. *Biosci. Biotechnol. Biochem.* **2013**, *77*, 217–223, doi:10.1271/bbb.120351.
123. Ghareeb, M.A.; Sobeh, M.; Rezaq, S.; El-Shazly, A.M.; Mahmoud, M.F.; Wink, M. HPLC-ESI-MS/MS profiling of polyphenolics of a leaf extract from *Alpinia zerumbet* (Zingiberaceae) and its anti-inflammatory, anti-nociceptive, and antipyretic activities in vivo. *Molecules* **2018**, *23*, 3238, doi:10.3390/molecules23123238.
124. Kumagai, M.; Mishima, T.; Watanabe, A.; Harada, T.; Yoshida, I.; Fujita, K.; Watai, M.; Tawata, S.; Nishikawa, K.; Morimoto, Y. 5, 6-Dehydrokawain from *Alpinia zerumbet* promotes osteoblastic MC3T3-E1 cell differentiation. *Biosci. Biotechnol. Biochem.* **2016**, *80*, 1425–1432, doi:10.1080/09168451.2016.1153959.
125. Burnett, C.; Valentini, S.; Cabreiro, F.; Goss, M.; Somogyvári, M.; Piper, M.D.; Hoddinott, M.; Sutphin, G.L.; Leko, V.; McElwee, J.J. Absence of effects of Sir2 overexpression on lifespan in *C. elegans* and *Drosophila*. *Nature* **2011**, *477*, 482–485.
126. Satoh, A.; Stein, L.; Imai, S. The role of Mammalian Sirtuins in the Regulation of Metabolism, Aging, and Longevity. In *Histone Deacetylases: The Biology and Clinical Implication*; Springer: Berlin/Heidelberg, Germany, 2011; pp. 125–162.
127. Grabowska, W.; Sikora, E.; Bielak-Zmijewska, A. Sirtuins, a promising target in slowing down the ageing process. *Biogerontology* **2017**, *18*, 447–476, doi:10.1007/s10522-017-9685-9.
128. Xuan, T.; Quan, N.; Quan, N.; Rayee, R.; Khanh, T.; Tran, H.; Trung, N. Allelopathic plants: 26. *Alpinia zerumbet* (Pers.) BL Burtt & RM Sm. (Zingiberaceae). *Allelopathy J.* **2019**, *48*, 1–13, doi:10.26651/allelo.j/2019-48-1-1239.
129. Kuraya, E.; Yamashiro, R.; Touyama, A.; Nakada, S.; Watanabe, K.; Iguchi, A.; Itoh, S. Aroma profile and antioxidant activity of essential oil from *Alpinia zerumbet*. *Nat. Prod. Commun.* **2017**, *12*, 1322–1325, doi:10.1177/1934578X1701200842.

130. Dias, D.M.; Costa, N.M.B.; Nutti, M.R.; Tako, E.; Martino, H.S.D. Advantages and limitations of in vitro and in vivo methods of iron and zinc bioavailability evaluation in the assessment of biofortification program effectiveness. *Crit. Rev. Food Sci. Nutr.* **2018**, *58*, 2136–2146, doi:10.1080/10408398.2017.1306484.
131. Roberts, A.E.; Kragh, K.N.; Bjarnsholt, T.; Diggle, S.P. The limitations of in vitro experimentation in understanding biofilms and chronic infection. *J. Mol. Biol.* **2015**, *427*, 3646–3661, doi:10.1016/j.jmb.2015.09.002.

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).