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Chapter

Bioinformatics Exploration of Ginseng: A Review

Toluwase Hezekiah Fatoki

Abstract

Ginseng contains an extraordinarily complex mixture of chemical constituents that can vary with the species used, the place of origin, and the growing conditions. Various computational analyses which include genomics, transcriptomics, proteomics and bioinformatics have been used to study ginseng plant. A genome-scale metabolic network offers a holistic view of ginsenoside biosynthesis, helps to predict genes associated with the production of pharmacologically vital dammarane-type ginsenosides, and provides insight for improving medicinal values of ginseng by genomics-based breeding. The draft genomic architecture of tetraploid *P. ginseng* cultivar (cv.) Chunpoong (ChP) by de novo genome assembly, was found to be 2.98 Gbp and consist of 59,352 annotated genes. Presently, bioinformatics exploration of ginseng includes studies on its P-glycoproteins, the impact of cytochrome P-450 on ginseng pharmacokinetics, as well as target prediction and differential gene expression network analyses. This study applauded Betasitosterol and Daucosterin as ginseng bioactive constituents that have several potential pharmacological effects in human, by modulating several proteins which include androgen receptor, HMG-CoA reductase, interlukin-2, and consequently impact the signaling cascade of several kinases such as mitogen-activated protein kinases (MAPKs), as well as many transcription factors such as polycomb protein SUZ12.

Keywords: Ginseng, bioinformatics, transcriptomics, genomics, bioactive, pharmacokinetics

1. Introduction

Ginseng is a slow-growing, deciduous, perennial plant of the *Araliaceae* family which includes *Panax ginseng* (*Renshen*, Chinese or Korean ginseng), *Panax japonicus* (Japanese ginseng) and *Panax quinquefolius* (*Xiyangshen*, American ginseng) among others [1]. Ginseng contains an extraordinarily complex mixture of chemical constituents that can vary with the species used, the place of origin, and the growing conditions [2]. Ginsengs has found therapeutic application such as anti-inflammatory, anti-haemostatic, antioxidant, anticancer, anti-diabetic, antiaging, anti-depressive, immunomodulatory, analgesic, neuroprotection, memory and learning enhancement effects in animals and humans [1, 3–7]. Various computational analyses which include genomics, transcriptomics, proteomics and bioinformatics have been used to study ginseng plant [4, 8–10].

1.1 Ginseng genomics and biosynthesis of ginsenosides

A genome-scale metabolic network offers a holistic view of ginsenoside biosynthesis, helps to predict genes associated with the production of pharmacologically vital dammarane-type ginsenosides, and provides insight for improving medicinal values of ginseng by genomics-based breeding [11]. The draft genomic architecture of tetraploid *P. ginseng* cultivar (cv.) Chunpoong, by de novo genome assembly, was reported to be 2.98 Gbp and consist of 59,352 annotated genes [11]. Recently, a dynamic database was built that integrates a draft genome sequence, transcriptome profiles, and annotation datasets of ginseng, which is publicly available (http://ginsengdb.snu.ac.kr/) for the use of scientific community around the globe for exploring the valuable resources for a range of research fields related to *P. ginseng* and few other species [4]. Transcriptome analysis has identified 100 *Panax ginseng* cytochrome P450 (*PgCYP*) genes, whose expressions were significantly correlated with variation of nine mono- and total-ginsenoside contents, while further association study identified five SNPs and three InDels from six *PgCYP* genes that were significantly associated with the ginsenoside contents in the four-year-old roots of 42 genotypes [9].

2. Ginsenosides: structure, pharmacokinetics and mechanism

Ginsenosides are specific types of triterpene saponin, a broad group of chemical compounds. Ginsenosides are found nearly exclusively in Panax species (ginseng) and up to now more than 150 naturally occurring ginsenosides have been isolated from different organs of ginseng [12]. Ginsenosides appear to be responsible for most of the activities of ginseng including anti-diabetic, anti-allergic, anticarcinogenic, anti-inflammatory, anti-atherosclerotic, antihypertensive, and immunomodulatory effects as well as anti-stress activity and effects on the central nervous system [6]. The structures of ginsenosides Rb1 and Rg1 are shown in **Figure 1**.

2.1 Structure of ginsenosides

Shi *et al*. [13] have reported that the seven major ginsenosides (Rg1, Re, Rb1, Rc, Rb2, Rb3 and Rd) were present in various parts of Chinese ginseng of various ages. Ginsenoside content is higher in the leaf and root hair but lower in the stem than that in other parts of the plant and that the total content of ginsenosides in the leaf decreases with age [1, 13]. Ginsenosides are divided into three main categories, the 20(S)-protopanaxadiol, 20(S)-proto- panaxatriol and oleanane families according

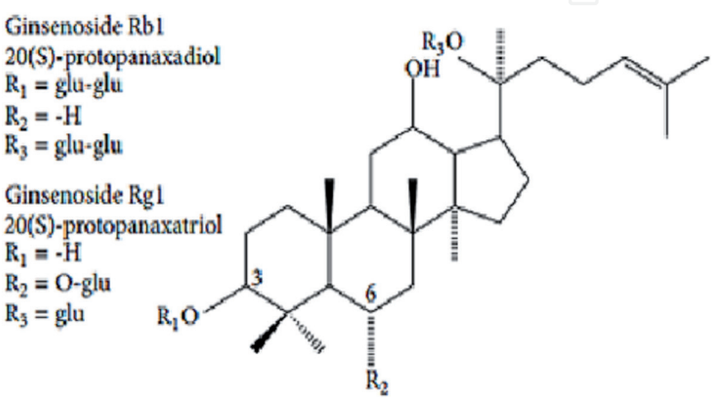

Figure 1.
Structures of ginsenosides Rb1 and Rg1. (Adapted from [5]).

to the number and position of sugar moieties on the sterol chemical structure. it is difficult to clarify the influence of the sugar moiety at different positions on pharmacological actions [14].

2.2 ADME of ginsenosides

Absorption, distribution, metabolism and excretion (ADME) describe the pharmacokinetics and pharmacodynamics of a single or more compounds in an organism such as human, mouse etc. The knowledge of pharmacokinetics of ginsenoside and its metabolites is very imperative in designing an optimal dosage regimen and minimizing the adverse effect that may result from ginseng-drugs interaction. The polar ginsenosides include Rg1, Re, Rb1, Rc, Rb2, Rb3, and Rd., while less polar ginsenosides include Rg2, Rg3, Rg5, Rh2, Rk1, and Rs4 [15, 16]. Protopanaxadiol ginsenosides are metabolized to ginsenoside compound K by the intestinal microflora in humans. Ginsenoside compound K (20-*O*-β-D-glucopyranosyl-20(S)-protopanaxadiol), is found in the blood stream of humans as an active metabolite after oral administration of protopanaxadiol ginsenosides Rb1, Rb2, Rc, and Rd., and has significantly higher mean maximum plasma concentration and significantly lower half-life when compare to the ginsenoside Rb1 [17].

According to Qi et al., [18], the ginseng saponins have low absorption rate and characterized by extensive metabolism in the gastrointestinal tract, poor membrane permeability, and low solubility of deglycosylated products; and with less than 5% dose bioavailability of the protopanaxadiol (PPD) group of saponins (ginsenosides Ra3, Rb1, Rd., Rg3, and Rh2) and of the protopanaxatriol (PPT) group of saponins (ginsenosides Rg1, Re, Rh1, and R1) were less than 5%. However, PPT saponins have better bioavailability than PPD saponins, which may be due to the fact that PPD saponins degrade faster than PPT saponins. Study on ginseng absorption by HPLC analysis, showed that Rb1 (4.35%) and Rg1 (18.40%) were absorbed, respectively [19].

Study on the effect of American ginseng and Asian ginseng extracts on gene expression of the hepatic cytochrome P450 enzyme in elderly humans, has shown that protopanaxadiol (PPD), protopanaxatriol (PPT) and their metabolites, moderately inhibited CYP2C9 activity and strongly inhibited CYP3A4 activity [20, 21]. Henderson et al., [22] have studied the effects of seven naturally occurring ginsenosides Rb1, Rb2, Rc, Rd., Re, Rf, and Rg1 and eleutherosides B and

S.No	Constituents	References
1.	Ginsenine	[24]
2	betasitosterol, 20(R)-protopanaxatriol, daucosterin, 20(R)-ginsenoside-Rg3	[25]
3	isoginsenoside-Rh(3), ginsenoside-Rb(1), -Rb(2), –Rc, –Rd, -Re, – Rg(1), -Rh(1), -Rh(2).	[26]
4	Daucosterin; 20(R)-dammarane-3beta,12beta,20,25-tetrol (25-OHPPD); 20(R)-dammarane-3beta,6alpha,12beta,20,25-pentol (25-OH-PPT); 20(S)-protopanaxadiol (PPD); 20(S)-ginsenoside-Rh(2) (Rh2); 20(S)-ginsenoside-Rg(3) (Rg3); 20(S)-ginsenoside-Rg(2) (Rg2); 20(S)-ginsenoside-Rg(1) (Rg1); 20(S)-ginsenoside-Rd (Rd); 20(S)-ginsenoside-Re (Re); 20(S)-ginsenoside-Rb(1) (Rb1).	[27]
5	Panaxadione, ginsenosides Rd., Re, and Rg2	[28]

Table 1.
Chemical constituents of P. ginseng.

S.No	Ginsenoside	Mechanism	Reference
1	Rb1	protects hippocampal neuron, enhance insulin/IGF-1 signaling, inhibited GSK-3β-mediated C/EBP homologous protein (CHOP) signaling	[29–32]
2	Rb_2	Down-regulation of matrix metalloproteinase (MMP)-2	[33]
3	Rg1	Downregulation of nuclear factor-kappa B (NF-κB)/nitric oxide (NO) signaling pathway, increases the expression of insulin growth factor I receptor (IGF-IR)	[34–35]
4	Rd	Phosphoinositide-3-kinase/AKT and phosphoextracellular signal-regulated protein kinase (ERK) 1/2 pathways, suppress poly(ADP-ribose) polymerase-1, protein tyrosine kinase activation, the upregulation of the endogenous antioxidant system and GAP-43 expression	[5, 36, 37]
5	Re	PREVENT the reduction of H(+)-ATPase activity	[38]
6	Rg3	Modulation of three modules of MAP kinases, P-gp (P-glycoprotein) inhibition, modulation of Ephrin receptor pathway, inhibits NMDA receptor by increasing the concentration of glycine, suppression of TPA-induced cyclooxygenase-2 (COX-2) expression	[39–42]

Table 2.
The molecular mechanism of ginsenosides pharmacological activities.

E (active components of the ginseng root) on the catalytic activity of *c*DNA expressed CYPs (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) in *in vitro* experiments. They found that the ginsenosides and eleutherosides tested are not likely to inhibit the metabolism of co-administered medications in which the primary route of elimination is via cytochrome P450 [22]. Comprehensive review of the ginseng active compounds pharmacokinetics, drug–drug interaction, and influence of cytochrome P450 has been published [23]. Chemical constituents of *P. ginseng* and mechanisms of selected ginseng compounds are shown in **Table 1** and **2** respectively.

3. Bioinformatics analyses of ginsenosides

A study has proposed a novel method to explore underlying mechanisms of multiple actions of multiple constituents of Ginseng (*Panax ginseng*) against cancers, and the bioinformatics analyses was initiated with proteins regulated by ginsenoside rb1/re/rg1, using standard tools such as ChEMBL, STRING, DAVID and KEGG [43].

In the study conducted by Yan et al. [44] to identify immunomodulatory biomarkers in an immune cell induced by ginseng, microarray assays were carried out to identify differentially expressed genes associated with American ginseng (*Panax quinquefolius*) exposure to 4 groups of Murine splenic cells from adult male C57BL/6 (B6) mice which were isolated to mimic 4 basic pathophysiological states. The microarray data obtained was analyzed with Partek Genomics Suite software while DAVID Bioinformatics Resources 6.7 was used for functional annotation clustering. The effect of American ginseng on the interferon gamma signaling functions was obtained by the use of Interferome software [44].

In their study, Zhu et al. [8], have reported two major *Panax ginseng* glycoprotein (PGG-1 and PGG-2) obtained by high performance liquid chromatography, with

the molecular weights of 1.5 KDa and 8.2 KDa respectively calculated by gel permeation chromatography. The ginseng samples were analyzed by LC–MS using a nano-flow RP-HPLC online-coupled to a Q Exactive mass spectrophotometer operating in the positive ion mode. The raw MS files were analyzed and searched against the UniProt ginseng protein sequence database using Byonic software (Version 2.3.5). The computed parameters of PGG determined by MS include theoretical isoelectric point (pI), instability index, aliphatic index and grand average of hydropathicity (GRAVY). The aliphatic index of PGG-1 ranged from 0 to 130, with an average of 48.23; the aliphatic index of PGG-2 ranged from 61.25 to 195.71, with an average of 129.41 [8].

Bioinformatics network analysis has been used to analyzed a combination of ginseng and arginine regimen, ginseng and lingzhi as well as ginseng and gingko regimens [45, 46], in order to understand potential impact of drug–drug interaction (agonism or antagonism) based on common pathways.

3.1 *In silico* target prediction and gene expression network of key ginseng constituents

The ligands (Ginsenoside Rb1, Rc, Rg3, Re, F1, C; Betasitosterol, Panaxadione, Daucosterin (also known as Sitogluside or Eleutheroside A), and 20(R)-protopanaxatriol) were subjected to *in silico* target prediction on Swiss TargetPrediction server where *Homo sapiens* was selected as target organism [47] as shown in **Table 3**. Forty-five (45) genes (PTAFR, IL2, STAT3, VEGFA, FGF1, FGF2, HPSE, PSEN1, PSENEN, NCSTN, BCL2L1, PRKCA, HSD11B1, CYP19A1, SIRT2, PTPN1, CCR1, VDR, PTPN11, NR1I2, REN, BACE1, NR3C1, INSR, ITK,

S.No	Constituents	Target Genes	% probability	Possible effect
1	Ginsenoside Rb1, Rg3, Rc, Re, F1, C,	PTAFR, IL2, STAT3, VEGFA, FGF1, FGF2, HPSE, PSEN1, PSENEN, NCSTN, BCL2L1	10	Immunomodulatory, anti-haemostatic, anti-cancer
2	Panaxadione	PRKCA, HSD11B1, CYP19A1, SIRT2, PTPN1, CCR1, VDR, PTPN11, NR1I2, REN, BACE1, NR3C1, INSR, ITK, F2R	20	Anti-inflammatory, anti-diabetic
3	Betasitosterol	AR, HMGCR, CYP51A1, NPC1L1, NR1H3, CYP19A1, CYP17A1, RORC, ESR1, ESR2	35–70	Anti-depressive, neuroprotection, anti-cancer
4	Daucosterin	STAT3, IL2	20–60	Immunomodulatory, anti-cancer, anti-inflammatory
5	20(R)-protopanaxatriol	PTPN1, CYP2C19, CHRM2, SLC6A2, SLC6A4, AR, ACHE, HSD11B1, ESR1, CYP19A1, ATP12A, NR1H3, HMGCR, CYP51A1, NPC1L1	20	Anti-depressive, anti-hypertension

Table 3.
Predicted genes of selected Ginseng constituent.

F2R, AR, HMGCR, CYP51A1, NPC1L1, NR1H3, CYP19A1, CYP17A1, RORC, ESR1, ESR2, CYP2C19, CHRM2, SLC6A2, SLC6A4, ACHE, HSD11B1, ATP12A, HMGCR, CYP51A1) were extracted from the predicted targets and subjected to expression network analyses (transcription factor enrichment analysis, protein–protein interaction network expansion and kinase enrichment analysis), using eXpression2Kinases (X2K) Web server [48] as shown **Figures 2-5**.

The genes that were targeted by Betasitosterol (**Table 3**) have greater than 30% probability (35–70%), Daucosterin targeted Interleukin-2 (IL2) with 60% probability, while others were less than 30%. The best target of Betasitosterol is Androgen Receptor (AR), followed by 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, Cytochrome P450 51, Niemann-Pick C1-like protein 1, LXR-alpha, Cytochrome P450 19A1, Cytochrome P450 17A1, Nuclear receptor ROR-gamma and others.

This study shows that SUZ12 has the highest score as transcription factor influenced by the ginseng, this is followed by STAT3, RUNX1, FOS, VDR, RCOR1,

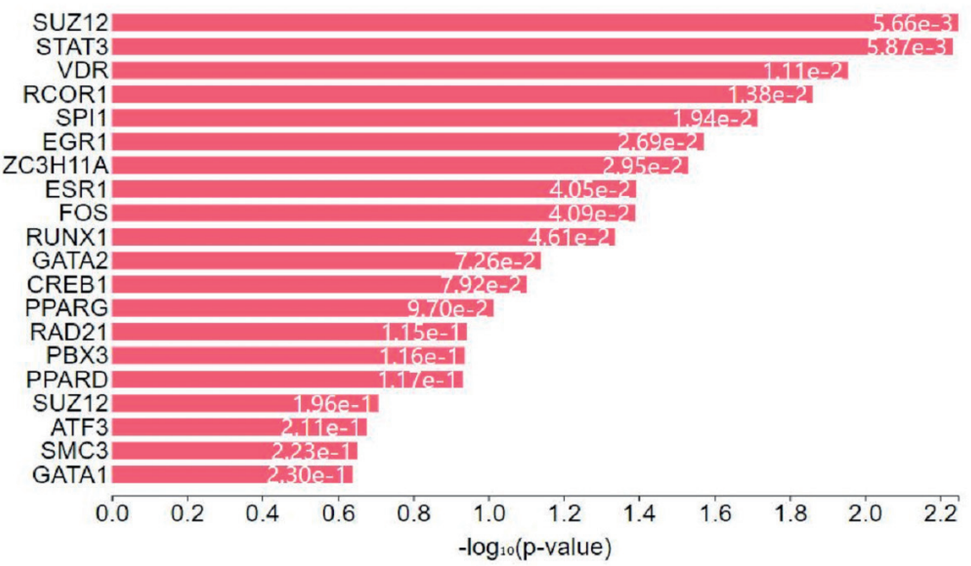

Figure 2.
Transcription Factor Enrichment Analysis (TFEA).

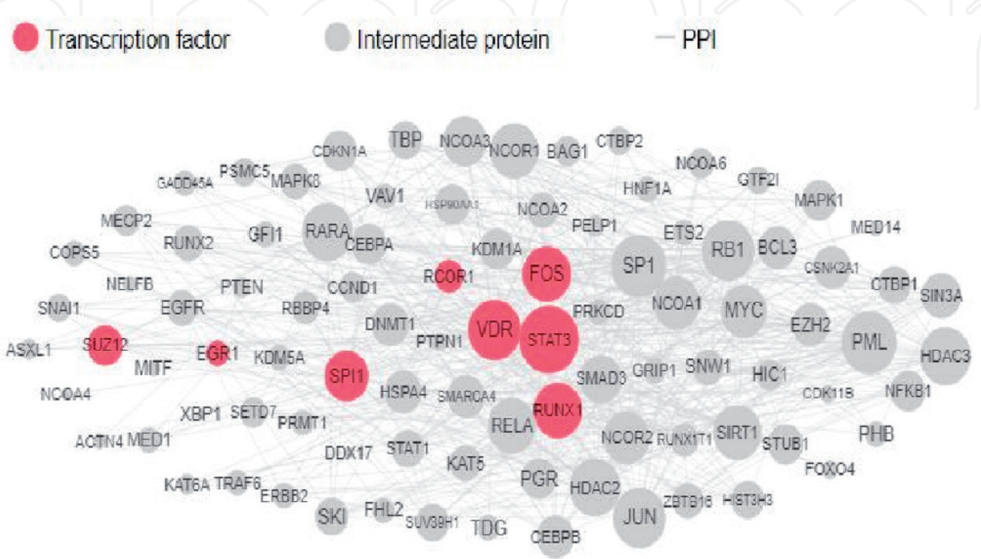

Figure 3.
Protein–Protein Interaction.

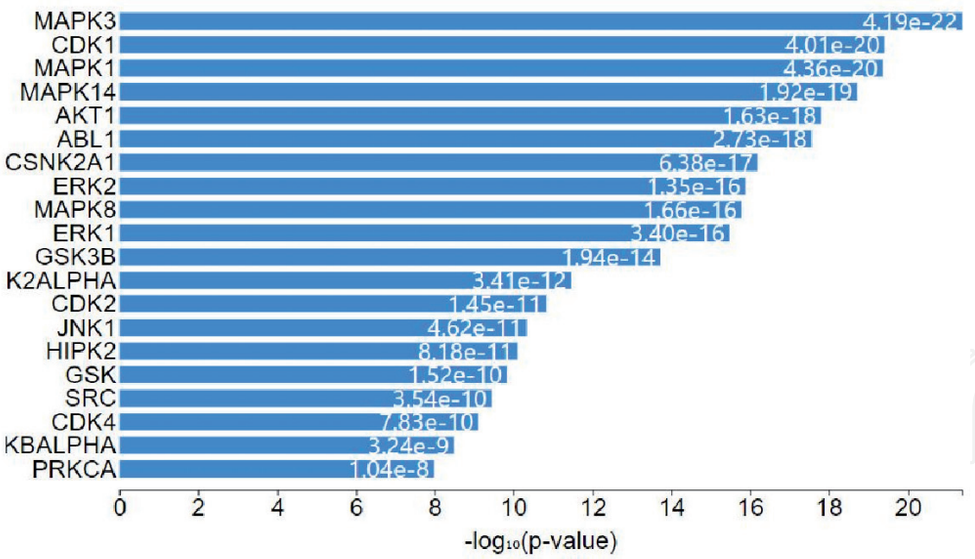

Figure 4.
Kinase Enrichment Analysis (KEA).

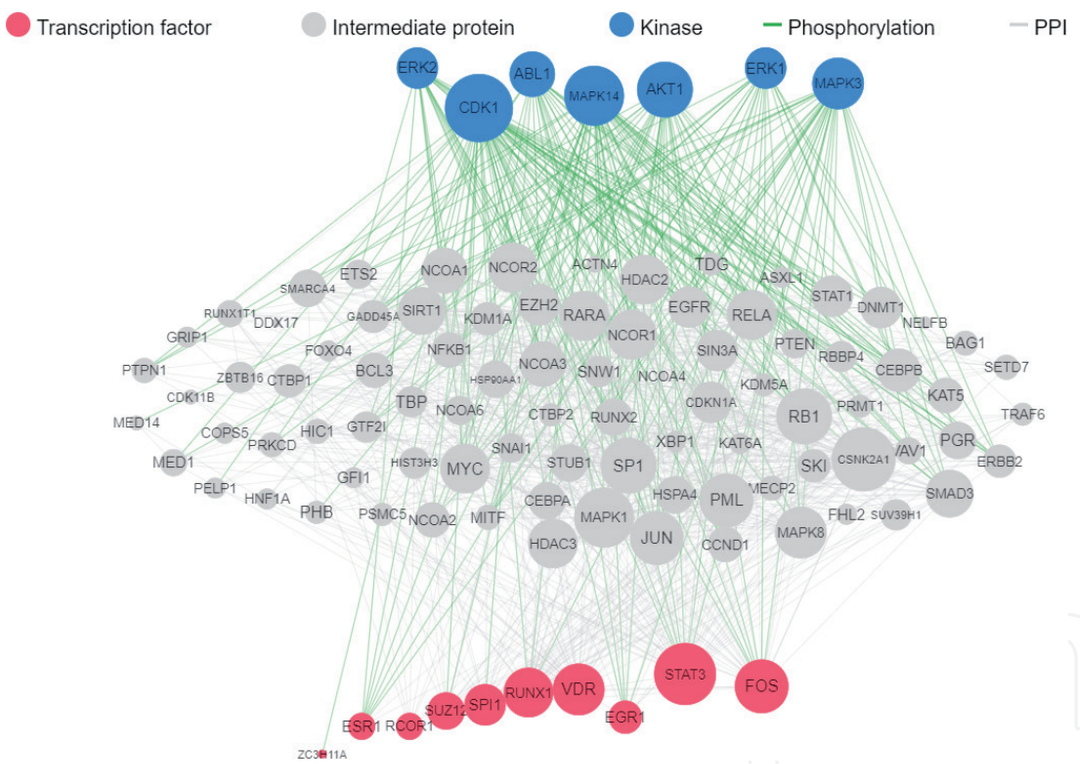

Figure 5.
eXpression2Kinases Network.

SPI1 and EGR1 (**Figures 2** and **3**). The kinases that were impacted by the action of ginseng active constituents include MAPK1, MAPK14, AKT1, CDK1, ABL1, ERK1 and ERK2 (**Figure 4**). Moreover, major intermediate proteins JUN, RARA, NCOR1, MYC, RB1, HDAC2, CSNK2A1 and others (**Figure 5**).

Zhang et al. [49] have reported ginsenoside, stigmasterol, β-sterol, β-elemene and β-selinene, kaempferol, panaxynol, ginsenoyne A, fumarine, girinimbin, elemicin, dauricine, and maltol, as part of secondary metabolites produced by ginseng. However, network analysis of ginseng-associated targets ginseng in treatment of depression which could occur in post-COVID19 period, identified AKT1, CASP3, NOS3, TNF, and PPARG as the core genes in protein–protein interaction network,

and that ginsenoside Re, ginsenoside Rg1, frutinone A and kaempferol were the key ingredients in ginseng for immune-regulation [50].

Based on curated data on UniProt database (www.uniprot.org), androgen receptor (Uniprot ID: P10275) involves in positive regulation of MAPK cascade, NF-kappaB transcription factor activity, insulin-like growth factor receptor signaling pathway, and transcription by RNA polymerase II and III, as well as negative regulation of transcription by RNA polymerase II, epithelial cell proliferation, and extrinsic apoptotic signaling pathway. HMG-CoA reductase (UniProt ID: P04035) involves in positive regulation of ERK1 and ERK2 cascade, stress-activated MAPK cascade, cardiac muscle cell apoptotic process, smooth muscle cell proliferation, and cholesterol homeostasis, as well as negative regulation of MAP kinase activity, wound healing, and striated muscle cell apoptotic process, and it also give response to ethanol. Interleukin-2 (UniProt ID: P60568) involves in positive regulation of inflammatory response, transcription by RNA polymerase II, tyrosine phosphorylation of STAT protein, interferon-gamma production, B cell and activated T cell proliferation and immunoglobulin secretion, as well as negative regulation of inflammatory response, heart contraction, B cell apoptotic process, and lymphocyte proliferation, and it also give response to ethanol.

A comprehensive review of betasitosterol has reported several therapeutic potentials which include antioxidant, antipyretic, anti-inflammatory, anti-arthritic, and antimicrobial activities, as well as anti-cancer, anti-diabetic, antihyperlipidemic, anti-atherosclerosis, anti-pulmonary tuberculosis, angiogenic, immune modulation and anti-HIV effects [51].

4. Conclusion

Knowledge of bioinformatics has not been fully applied to the study of ginseng in proportionality to the acclaimed medicinal properties from the ethnobotanical use.

This study has applauded Betasitosterol and Daucosterin as ginseng bioactive constituents that have several potential pharmacological effects in human, by modulating several proteins which include androgen receptor, HMG-CoA reductase, interlukin-2, and consequently impact the signaling cascade of several kinases such as Mitogen-activated protein kinases (MAPKs), as well as many transcription factors such as Polycomb protein SUZ12. Moreover, difference in pharmacological outcome of aqueous ginseng extract and ethanolic ginseng extract would necessitate holistic approach of extraction. Furthermore, chemical biology and *in silico* simulation of pharmacological potential of ginseng bioactive compounds (such as molecular docking and dynamics, drug–drug interaction) will yield significant insights to the presently unexplored molecular mechanisms of action to explain the therapeutic effect of ginseng.

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Conflict of interest

The authors declare no conflict of interest.

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Author details

Toluwase Hezekiah Fatoki
Department of Biochemistry, Federal University Oye, Oye-Ekiti, Ekiti State, Nigeria

*Address all correspondence to: toluwase.fatoki@fuoye.edu.ng; hezekiahfatoki@gmail.com

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