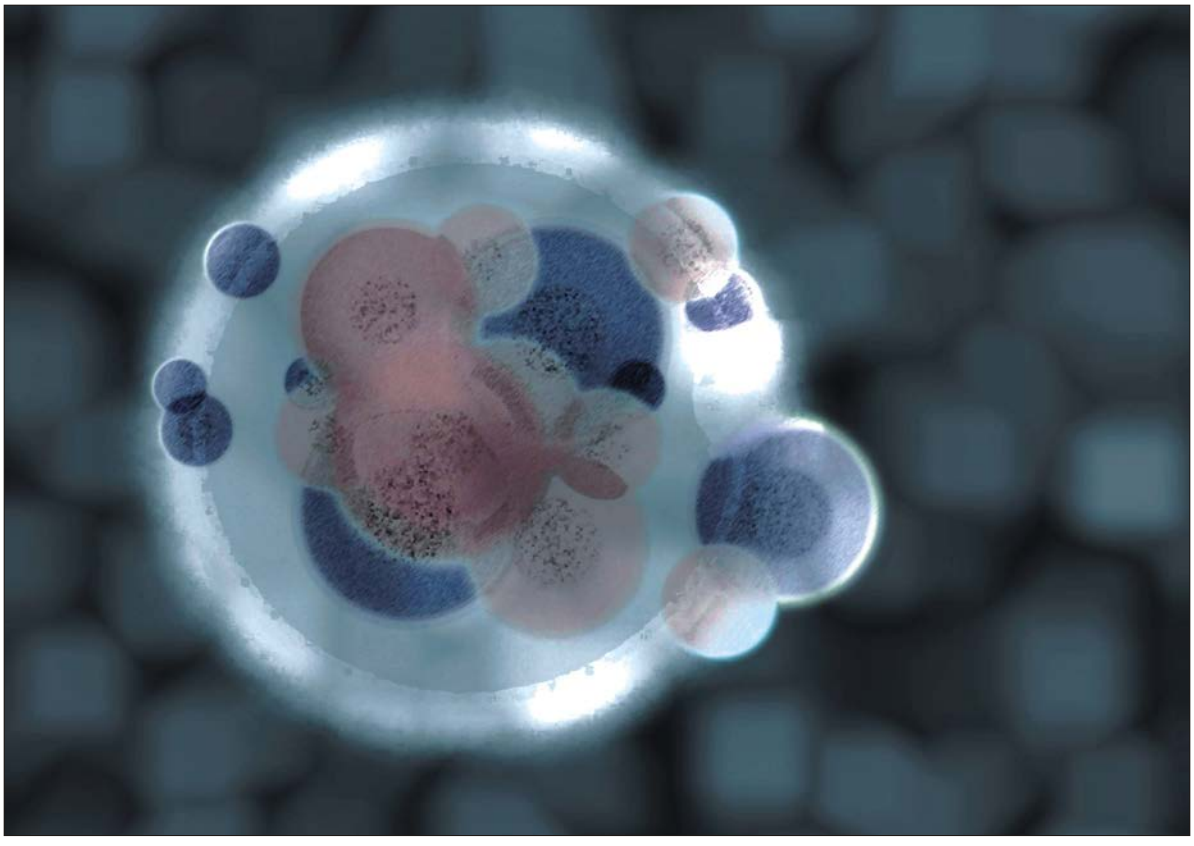

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Review Article
Gene Level Interactions of Four Commonly Used Herbal Products-A Systematic Literature

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Abstract

Increasing discoveries and introduction of new technologies in genomics field has shown that genomic variations can cause important differences in effects and efficiency of drugs. Thus, the assessment of herbal interactions at gene level can shed light on how effects and efficiency of herbal products (HP) are changed due to genomic variations. In this review, the studies focusing on interactions of four commonly used and clinically important HP, St. John's wort (*Hypericum perforatum*), Ginkgo (*Ginkgo biloba*), Ginseng (Panax ginseng) and Kava (*Piper methysticum*) with genomic variations by performing a systematic literature review of PubMed database covering the period from the dates of database's inception till end of 2016 were investigated. The articles met inclusion criteria were classified according to design of studies. The search and evaluation of thousands of articles brought only 15 articles particularly focusing on interaction of four selected HP with genomic variations in certain genes. Of these 15 articles elaborated in this study 11 performed on human subjects while animal models used in 3 of them. And only 1 study was conducted using cell lines. In total, 17 genes were reported in these studies while one of them was genome wide association study. Although it is known that HP interact with numerous number of genes and genomic variations can alter the efficacy, results of our study have showed these pharmacogenomic mechanisms are poorly investigated. Therefore, comprehensive studies focusing on gene level interactions are strongly needed to improve safety and efficiency standards for HP.

Key words: Genomics, ginkgo, ginseng, kava, St. John's wort

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

As natural substances derived by minimal or no industrial processing of medicinal plants[1], herbal products (HP) are employed to prevent or treat a broad range of health conditions such as cardiovascular diseases[2], cancer[3] and neurodegenerative disorders[4]. Particularly in industrialized countries, use of HP with or instead of conventional drugs have become widespread in recent years. According to World Health Organization (WHO), approximately 80% of the world population uses herbal medicines and this percentage is even higher in developed countries[5]. However, lack of common standards and regulations increases concerns with safety and efficacy of HP[6]. While popularity and market of these products grow rapidly, comprehensive studies are indispensable to evaluate their potential risks and benefits.

Some of HP is known to not cause adverse effects whereas others have interactions and potentially, negative outcomes[7]. Especially identification of delayed and long term effects may not be detected during test of time and cause serious clinical consequences[8]. Interaction between HP and conventional drugs which can occur through various mechanisms[9] have often underestimated adverse effects[10] because of the standardization problems and lack of information among clinicians and consumers[11]. In addition, herb-drug interaction studies show the difficulty of obtaining standard results since HP includes variable mixtures of bioactive ingredients[12,13] and pharmacogenetic profiles differ among individuals[14,15].

Ginseng (*Panax ginseng*), Ginkgo (*Ginkgo biloba*), Kava (*Piper methysticum*) and St. John's wort (*Hypericum perforatum*) are commonly used HP worldwide[16-19]. Ginseng has been used for thousands of years as medicine in different countries[20]. Currently, it has one of the largest market sizes among HP and a continuous expansion in its market is expected coming years[21]. Although there are not convincing clinical efficacy results for all of them, Ginseng has been used for a variety of conditions such as common cold[22], erectile dysfunction[23], cancer[24], hypertension[25,26], cardiovascular diseases[27]. Moreover, it is also well known that Ginseng interacts with conventional drugs[28]. Ginkgo, a worldwide popular herb which originates from China[29], has been used for treatment of asthma, ischemia and lung congestion, dementia, sexual dysfunction and cognitive impairment[30]. Additionally, due to its bioactive ingredients such as kaempferol, quercetin, Ginkgo and the acylated flavonol glycosides Q- ag and K-ag, Ginkgo is used as an anti-diabetic, cardio and hepatoprotective drug. It also has antiproliferative and chemo-preventive feature which make it important for cancer therapies[31]. There are many reports on interaction between Ginkgo and different drugs and its effect mechanism on human metabolism[32-35]. As one of the most commonly used HP, St John's wort derived from an herbaceous perennial plant native to Europe and Asia[36]. In addition to its extensive use in depression, it has been also used for the treatment of excitability, neuralgia, fibrositis, sciatica, menopausal neurosis, anxiety and depression and as a nerve tonic and preparations for wound healing[37]. A number of studies on its chemistry, pharmacology and clinical pharmacokinetics have shown that St. John's wort interact with a number of conventional drugs and have effects on different metabolites and enzymes[38-41]. Kava, as a traditional drink in Pacific Islands for many years[42], has become popular with its sedative, anti-stress and anxiolytic properties due to about 18 kavalactone compounds forming its structure[43]. The interactions between Kava and conventional drugs have been well studied especially its effects through inhibition of cytochrome P 450 (CYP 450)[44].

Despite the fact that it is well known the efficiency and potential effects of these HP can show profound differences due to genomic variations among individuals, their effects and interactions at gene level have been poorly investigated. Thus, aim of this review is to explore studies specifically focusing on interactions of these HP with genomic variations and present the advances from genomic perspective.

MATERIAL AND METHODS

There have been plenty of research studies, reviews and databases focusing general or specific interactions of HP. By cause of concepts and extent of preferred sources, classes and number of interactions may show differences. Considering goals and criteria of the review and also to skip variable filtering steps, the recently published systematic review "Herb-drug interactions: An overview of systematic reviews" by Posadzki *et al.*[19] has been chosen as base in the selection of HP for the conducted study. In this review, it has been stated that four commonly used HP (Ginseng, Ginkgo, St. John's wort and Kava) which were chosen for this study are relatively more important in clinical consequences of their interactions by a comprehensive comparison and evaluation of systematic reviews on interactions of HP. In addition, these herbs have been traditionally used for centuries and become popular worldwide in last decades. For example, Ginseng is being purchased in 35 countries and considered as one of the most commonly used HP[21]. St. John's wort is currently used in many countries and it is among most commonly distributed HP as antidepressant in USA and European countries[45]. Ginkgo and Kava are also commonly known and sold HP in different

countries of the world[29,43]. Furthermore, wide range effects and myriad studies from different perspectives fit with starting point, flow and goals of the review. A diagram showing flow and scope of the study had been presented below in Fig.1.

A National Center for Biotechnology Information (NCBI) PubMed search covering the period from the dates of database's inception till end of 2016 was performed to identify all articles focusing on interactions of Ginseng (*Panax ginseng*), Ginkgo (*Ginkgo biloba*), St. John's Wort (*Hypericum perforatum*) and Kava (*Piper methysticum*) with genomic variations. 2009 PRISMA statement was chosen as a guideline for conducting the review[46]. The articles published in English language were included for review processes. Firstly, an electronic literature search was conducted to determine all articles including common or scientific name of HP to obtain all references consisting of interactions, biochemical or molecular properties, phylogenetic features, history and usage etc. In primary filtering step, the studies focusing on genomic variations-HP interaction were separated from other studies by use of filtering keywords "genomics", "polymorphism", "SNP", "population", "genotype", "pharmacogenomics", "personalized medicine", "variation", "allele", "gene", "exon", "intron", "homozygous", "heterozygous", "mutation", "nucleotide", "sequencing", "expression" and "chromosome" together with names of HP. The common and scientific name of each HP in quotation marks and mentioned keywords in quotation marks were used to construct search terms anywhere in articles. The operator AND was used between HP and other keywords to search articles including all search words. All articles included in this study can be reached by NCBI PubMed search with the specific information given in the review. In secondary filtering step, abstracts of the articles listed by mentioned search terms were read and ones met exclusion criteria were removed. The scope of this review covers only studies investigating potential interactions of HP with genomic variations of the subjects (human populations, model organisms, cell lines etc.,) administrated with these HP which might cause change in efficacy and outcomes of the treatment. To be further evaluated in the review process, design of an article must include, (i) Treatment of subject groups having different genetic variations with selected HP or (ii) Treatment of subjects with selected HP and a conventional drug to evaluate efficacy due to genetic variation profile of the subjects or (iii) Treatment of subjects to investigate changes in the expression level of certain genes assumed to effect efficacy of HP and search for association of gene polymorphisms manipulating these interactions or (iv) Genome wide association study for selected HP or (v) Study of interaction between polymorphisms of genes encoding drug metabolizer enzymes and HP. Thus, the articles on protein level interactions, intraspecies or interspecies genomic variation, molecular biological mechanisms, interaction with conventional drugs, biochemical features, history, statistics, phylogenetics, direct usage (not focusing on effects of genomic variations) and identification of selected HP were excluded in secondary filtering step. Since it was not possible to assess the potential for bias in the investigated studies, this step was not conducted. The final articles were read in depth, classified into 3 groups: Performed on human subjects, cell lines or animal models.

RESULTS AND DISCUSSION

In total, 15215 articles including Ginkgo, Ginkgo, St. John's Wort or Kava were obtained with as a result of NCBI PubMed search. The article lists obtained after filtering according to the mentioned search strategy have been shown in Additional File 1-4. The 2704 articles have been reviewed to examine if a gene level study has been performed. Removal of excluded articles after reading abstracts resulted 16 articles-one article was excluded since full-text article could not be obtained- on genomic variations-HP interactions. The final 15 articles were read in depth and classified. The classification process resulted that 11 article on human subjects, 3 studies on animal models and 1 performed on cell lines. Genes studied in final reviewed articles have been presented in Table 1 below. A detailed review of the final articles was performed and current advances in the field have been presented for each HP.

Ginseng: Almost 50% of articles (n = 7518) obtained through literature search are studies examining properties and activity of Ginseng which showed it was most popular one among chosen HP. On the other hand, changes in Ginseng efficacy according to genomic variations were found to be poorly studied. Using the filtering words mentioned in Fig.1 in title and abstracts of screened articles, the number of articles decreased to 1471. Inspection of 1471 articles containing keywords showed that only 24 articles focus on analysis of gene expression or genomic variations. Since it should be noted that the goal was to determine articles on potential modifying effects of genomic variations on HP efficiency not gene expression studies, only one of these articles fit with the scope of the review. As expected by authors of the review, although there were plenty of studies on ginseng, there was almost no study on its interaction with genomic variations.

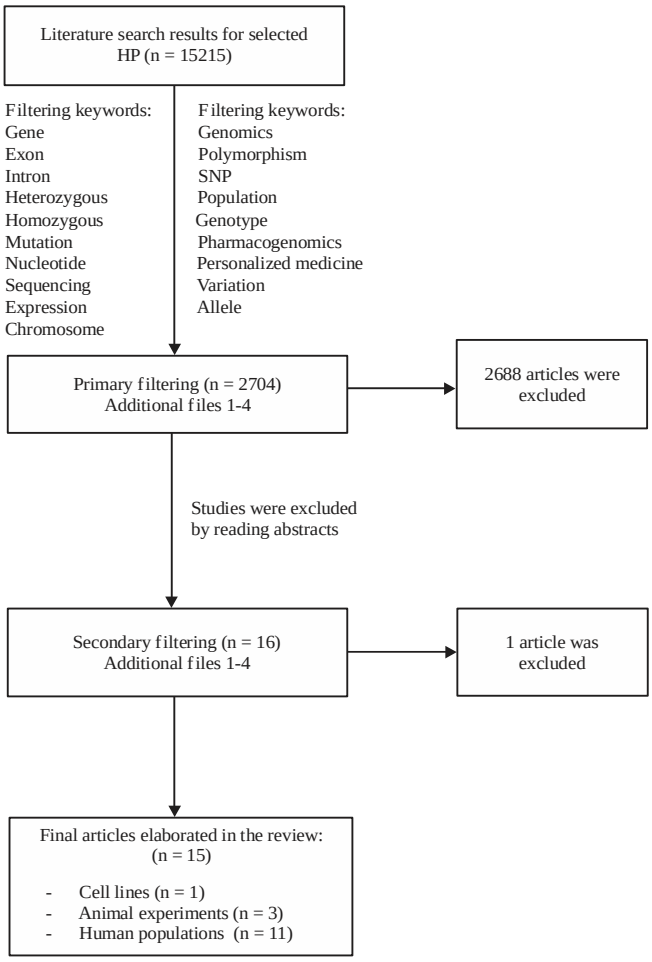

Fig. 1: Flow diagram of the study

Table 1: Genes studied in 15 reviewed articles

Herbal product	Genes	References
Ginseng	ADRB3, GNB3, ACE	Kwon *et al.*[47]
Ginkgo	$GABA_A$	Thompson *et al.*[48]
	BDNF	Zhang *et al.*[49]
	CYP2C19	Lei *et al.*[50]
	CYP2C19	Yin *et al.*[51]
	CYP2C19	Hong *et al.*[52]
St. John's wort	Ribosomal protein S29, Ribosomal protein S4, Microtubule associated protein 1a (MAP1A), LINE1 rev transcr. homolog, Carnitine palmitoyltransferase 1B, Humanin 1	Wong *et al.*[53]
	Genome wide association study	Rahmioglu *et al.*[54]
	PXR	Wang *et al.*[55]
	MDR1	Schwarz *et al.*[56]
	CYP1A1	Schwarz *et al.*[57]
	CYP2C9	Xu *et al.*[58]
	CYP2C19	Wang *et al.*[59]
Kava	SLC6A2	Sarris *et al.*[60]
	SLC6A2	Sarris *et al.*[61]

In the study chosen for further inspection, Kwon *et al.*[47] investigated effects of use of Korean red ginseng (KRG) (*Panax ginseng*) on obese women through its relation with polymorphisms in beta 3 adrenergic receptor gene (ADRB3), G protein beta 3 gene (GNB3) and angiotensin I converting enzyme gene (ACE) gene. It had been reported by different studies that single nucleotide polymorphisms (SNP) in ADRB3, GNB3 and ACE genes having important role in Resting

energy expenditure (REE) mechanism are associated with obesity risk[62]. Moreover, ginseng was used in the treatment of obesity as an efficient herbal product[63]. Thus, the research group investigated if the efficacy of KRG changes due to polymorphisms in mentioned genes. Similar studies for conventional drugs used for obesity treatment were performed and association between certain polymorphisms and efficiency of these drugs were confirmed[64]. In their study, Kwon *et al.*[47] has shown that KRG's efficacy on improvement of obesity differs significantly due to the C825T polymorphism at GNB3 gene. CT and TT alleles were shown to increase obesity risk and the results of this study were consistent with previous studies. The systolic blood pressure measurements showed significant difference between CT and CC (non-mutation) genotypes according to KRG administration. The KRG caused a decrease in blood pressure of CT genotype while no difference observed for CC genotype. Reducing food intake for CC genotype did not affect the differences between results of genotypes. It was concluded that KRG is more effective in T allele carriers for improvement of obesity. For ADRB3, Trp64/Arg heterozygous mutation carriers were found to have lower high density lipoprotein (HDL) than Trp64/Trp64 genotype carriers. However, other obesity indices did not confirm this difference possibly due to weak association of ADRB3 polymorphisms with obesity and low number (n = 5) of subjects carrying the mutation genotype is low. For ACE gene polymorphisms, although a significant improvement was observed in subjects with DD homozygote mutation according to KOQOL scale and a slight difference was noted for ID or non-mutation genotype, these results were not confirmed by other obesity indices. Thus, authors mentioned that it had not proven precisely that gene mutations altered the effects of KRG on improvement of obesity.

Ginkgo: Literature search brought 3934 articles including keyword "Ginkgo" or "*Ginkgo biloba*" of which 710 articles included filtering words used. 5 articles had been chosen to be reviewed in this study after examination of these articles.

Thompson *et al.*[48] investigated why *Ginkgo biloba* extracts have toxic effects in insects but not in humans and found that a single amino acid difference in $GABA_A$ receptor gene plays an important role in determination of toxicity of this herb. $GABA_A$ is one of neuronal receptors employed in vertebrate central nervous system and an important target for conventional drugs used for neurological disorders. Since *Ginkgo biloba* is commonly used for its neuroprotective effects, a potential interaction through $GABA_A$ gene was inspected. Results of the study revealed that an amino acid difference at second position of $GABA_A$ gene causes huge difference in the consequences of *Ginkgo biloba* treatment in insects and humans. Insects carry an Alanine amino acid in second position of their $GABA_A$ while humans have Valine amino acid. This single amino acid difference causes thousands fold change in efficacy of this herbal extracts. By showing how small variations in gene level can cause substantial differences in phenotype, the results of this study obviously support idea of this review as comprehensive studies are required to fully understand working mechanism and interactions of herbs to bring safer guidelines for usage these products.

Zhang *et al.*[49] conducted a study examining effects of *Ginkgo biloba* leaf extract EGb-761 on Tardive Dyskinesia (TD), a neurological disorder causing involuntary, repetitive body movements, hypothesizing it causes an increase in levels of brain-derived neurotrophic factor (BDNF) in serum and reduces TD especially in presence of Val66Met polymorphism in BDNF. Because of *Ginkgo biloba*'s known neuroprotective effects on central nervous system (CNS) and possible association between serum levels of BDNF and TB pathophysiology in earlier studies, an interaction between *Ginkgo biloba* and BDNF was investigated. Potential effect of a polymorphism (Val66Met) of BDNF gene on Ginkgo efficiency in treated patients. The genotypes were determined in Chinese schizophrenic patients with or without TD and healthy subjects. In a double-blind, randomized, placebo-control 12-week treatment with 240 mg per day of EGb-761 approximately 50 % of TD patients were studied to measure serum levels of BDNF after treatment. Abnormal Involuntary Movement Scale (AIMS) was used to measure clinical efficacy. It has been found that AIMS score is affected by presence of Val/Val allele and Met/Met allele. Thus, it was concluded that TD could be reduced in patients with Val/Val allele at BDNF gene more efficiently and genetic variation has an important role in activity of *Ginkgo biloba* but further investigations focusing on relation of analyzed polymorphism with serum BDNF levels and *Ginkgo biloba* treatment efficiency need to be performed.

In another study, Lei *et al.*[50] examined the possible different effects of *Ginkgo biloba* on voriconazole, an anti-fungal drug, in Chinese volunteers having poor metabolizer genotype of CYP2C19 (2C19*2/2C19*2) and volunteers having extensive metabolizer genotype of CYP2C19 (2C19*1/2C19*1). 40 extensive metabolizer volunteers were compared with 7 poor metabolizer volunteer. Both groups were administered by voriconazole and Ginkgo twice per day for 12 days. Obtained results of the study showed that Ginkgo did not affect pharmacokinetics of

voriconazole significantly since there were no significant change between poor and extensive metabolizer genotypes. On the other hand, it was mentioned that the study focused on CYP2C19 genotypes and another CYP enzyme could affect the results. Moreover, the results could not be applied for all *Ginkgo biloba* products. Still, the design of the study points importance of the study of herb-drug interaction through effects of genotypes. To investigate potential interaction between omeprazole, a proton pump inhibitor used in treatment of several diseases and *Ginkgo biloba* Yin *et al*.[51] compared hydroxylation rates of omeprazole by induction of *Ginkgo biloba* due to differences in CYP2C19 genotypes. A correlation has been determined between *Ginkgo biloba* induction of omeprazole according to poor and extensive metabolizer genotypes. Omeprazole level in plasma decreases fastest in homozygote extensive metabolizer and lowest in poor metabolizer genotype. This study showed that *Ginkgo biloba* affects omeprazole due to different genotypes. Hong *et al*.[52] determined the platelet aggregation ability of clopidogrel (an antiplatelet agent that inhibits blood clots), ticlopidine (an antiplatelet agent that inhibits blood clots) and ticlopidine plus *Ginkgo biloba* extract due to different genotypes. Results of this study revealed that while clopidogrel responsiveness was significantly affected by CYP2C19 *2 alleles, ticlopidine plus *Ginkgo biloba* causes enough platelet aggregation with tolerable adverse effects and was not affected by determined allelic profiles. Although it included a mix of Ginkgo and ticlopidine which could seriously cause differences in results, it may gave an idea about whether Ginkgo efficacy was not affected by these genetic polymorphisms.

The investigation of studies on potential interactions of *Ginkgo biloba* with genomic variations showed that 4 of studies focused on CYP2C19 genotypes and interaction with conventional drugs when used together. The results showed differences between studies which might resulted from Ginkgo product used for the study (although *Ginkgo biloba* species was employed in all studies), focus on the same gene without considering the other CYP enzymes and specific working mechanism features for each conventional drug. Studies with large number of subjects and several candidate genes and polymorphism in controlled study designs were needed to investigate the role of *Ginkgo biloba* used with/without conventional drugs.

St. John's wort: Although number of studies on St. John's wort was less than half of the number of studies on Ginseng, it had highest relative ratio of genomic perspective studies when compared. 2949 articles including keyword "St. John's Wort" or "*Hypericum perforatum*" were filtered and 398 articles had been chosen for further investigations. After examination of these articles, 7 of them had been reviewed in detail due to their relevance.

Wong *et al*.[53] studied effects of tricyclic antidepressant St. John's wort and imipramine on rat subjects to examine if they share a similar pattern as antidepressant products in gene expression. Novel candidate genes had been determined for both compounds. Investigation of six common genes (Ribosomal protein S29, Ribosomal protein S4, Microtube-associated protein 1a, LINE1 rev transcr. homolog, Carnitine palmitoyltransferase 1B, Humanin 1) showed presence of single nucleotide polymorphisms in human orthologs of these genes. Results of the study showed that there might be an interaction between St. John's wort and polymorphisms of human orthologs of the mentioned genes. Accordingly, the reason of including this gene expression study in the final articles list was that authors of the study suggest polymorphisms in the studied genes could be targeted in future by pharmacogenomic studies. Taken together, it could be stated that new studies particularly investigating positive or negative effects of these polymorphisms on the efficiency of St. John's wort treatment for human subjects could reveal potential associations and contributed more effective and conscious use of this HP by consideration of profile of associated gene variants.

In a point of view as genome wide association study (GWAS) Rahmioglu *et al*.[54] searched for common genetic variations related to activity of CYP3A4, one of the most important drug metabolizing enzymes, induced by St. John's wort in 310 twins. Considering there is no important variation in this enzyme, authors decided to inspect other possible genetic loci modifying induction levels of CYP3A4. Although no significant variant association detected in induced CYP3A4 activity, the study is important as a GWAS design on St. John's Wort's relations with genetic variations. Another study focusing on PXR gene variations and their role in induction of CYP3A4 by St. John's wort was performed by Wang *et al*.[55]. The results showed that the variations in PXR gene have potential to change inducing ability of St. John's wort which presented necessity of studies about use of St. John's wort together with conventional drugs and optimal dosing.

Schwarz *et al*.[56] studied the consequences of St. John's wort usage in long term on pharmacokinetics of talinolol to search for P-glycoprotein expression changes. Authors concluded that polymorphisms detected in MDR1 gene affects induction of oral talinolol disposition by this HP which was associated with induction of MDR1 mRNA and P-glycoprotein

level. MDR1 genotypes in exon 12 (1236C>T), 21 (2677G>T/A), or 26 (2677T>A), that seems to determine the magnitude changes of consequences of St. John's wort. In a more recent study by Schwarz *et al.*[57] potential interaction between different polyphenols including St. John's wort and certain CYP1A1 genotypes associated with estrogen related cancers in several epidemiological studies were examined and it had been revealed St. John's wort's inhibition effect strongly depends on CYP1A1 genotype. These results suggested genotype-dependent activation of these compounds may not be only effector on estrogen-mediated diseases and natural polyphenols included in the diet and drugs may play an important role too.

Xu *et al.*[58] conducted a study on potential interaction of gliclazide with this HP in the human subjects having different CYP2C9 genotypes. According to results, St. John's wort caused clearance of gliclazide significantly but this effect was not dependent on CYP2C9 genotypes.

Wang *et al.*[59] studied the change in the activity of CYP2C19 due to the use of St. John's wort and CYP1A2 was used as control. It was known that St. John's wort interacts with cytochrome P450 and this interaction was the main reason of its effects on conventional drugs. In the study, 6 healthy adult men subjects having poor metabolizer vs. extensive metabolizer CYP2C19 genotype versus 6 healthy adult men having CYP2C19 were compared and it was shown that CYP2C19 activity was increased by this HP in extensive metabolizers while no change observed in poor metabolizer. These results showed that gene level interactions of St. John's wort should be considered by clinicians.

Since it was well known that St. John's wort interacted with CYP enzymes, most of the studies focused on this relation. On the other hand, extending the scope of the studies to new genes connected with these enzymes carries potential to shed light on working mechanism and interindividual variation in St. John's wort in different scenarios. To find optimal dosing and treatment options, both key regulators and their effect mechanisms had to be revealed with studies performed genome wide level.

Kava: The 814 articles had been obtained in first step literature search of Kava least studied HP among others. After same filtering steps with other HP, this number decreased to 125. Further investigations left 2 articles to be reviewed in concept of this study.

In first study, Sarris *et al.*[60] compared Kava and a benzodiazepine in their acute neurocognitive, anxiolytic and thymoleptic effects. Authors also examined potential effects of genetic polymorphisms on response to compared substances. Although it had been mentioned that results were imprecise because of sample size limitations, authors found that solute carrier family 6 (neurotransmitter transporter), member 2 (SLC6A2) polymorphisms may had an important role on response to kava. The second double-blind, randomized, placebo-controlled study performed by Sarris *et al.*[61] focuses on kava treatment efficacy for generalized anxiety disorder with 75 subjects. Participants were administered with an aqueous extract of kava (120/240 mg of kavalactones/day according to response) versus placebo for 6 weeks. Hamilton Anxiety Rating Scale (HAMA) was used to measure anxiety reduction during treatment while variations in noradrenaline and γ-aminobutyric acid (GABA) transporter genes genotyped to search for a potential association. Results of study demonstrated the difference between kava group and placebo group. It was concluded that kava had a reduction effect on anxiety compared with placebo group. Moreover reduction levels for kava treatment were associated with polymorphisms of GABA transporter (rs2601126, rs2697153) which showed genomic variants change response to kava treatment. Findings obtained in these studies about polymorphisms provided a useful genomic perspective for kava treatment in addition to its main results.

CONCLUSION

In conclusion, although a large number of studies had been performed on selected HP from different perspectives, a few of them investigated possible gene level interactions. Among evaluated 13270 articles, it had been found that only 16 (about 0.12% of total) studies focused these interactions and potential outcomes. After final filtering step, 15 articles were elaborated with exclusion of one article. 11 of reviewed studies performed on human subjects while animal models used in 3 of them. One study was conducted using cell lines. Most of the studies were performed to reveal potential interaction of HP with genes encoding drug metabolizing enzymes and provided results showing differences according to design of study, number of subjects, type of conventional drug used in combination with HP. Of note, although during the review process approximately 100 articles addressing gene expression alterations due to HP were screened, they were excluded in final filtering step because the goal of this review was to search for only the studies about interaction of genomic variations with selected HP. As expected by authors, there was almost no study on this important topic which pointed serious concerns about safety and efficacy problems considering the market of HP had been growing

continuously. It was well known that genomic variations could altered the effects of HP and clinical outcomes and there were numerous interactions between HP and genes. However pharmacogenomic mechanisms are poorly examined and understood contrary to conventional drugs while popular HP were purchased more than well-known conventional drugs in many countries without prescription which caused an uncontrolled treatment process and unpredicted consequences. Particularly, new genomic technologies like next generation sequencing or microarrays could be employed to conduct genome level screenings in large populations to determine potential interactions with genomic variations. Controlled, well designed and comprehensive studies employing new high throughput technologies may provide new horizons in this field. Taken together, purpose of this review was to receive attention to the lack of comprehensive studies in this field and discussed the current status of four commonly used and studied HP from genomic perspective. Further investigations were strongly needed to solve increasing concerns about safety and efficacy of HP and investigations from genomic perspective present an important part of this concept.

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