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A Novel Discovery: Holistic Efficacy at the Special Organ Level of Pungent Flavored Compounds from Pungent Traditional Chinese Medicine

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Abstract: Pungent traditional Chinese medicines (TCMs) play a vital role in the clinical treatment of hepatobiliary disease, gastrointestinal diseases, cardiovascular diseases, diabetes, skin diseases and so on. Pungent TCMs have a vastness of pungent flavored (with pungent taste or smell) compounds. To elucidate the molecular mechanism of pungent flavored compounds in treating cardiovascular diseases (CVDs) and liver diseases, five pungent TCMs with the action of blood-activating and stasis-resolving (BASR) were selected. Here, an integrated systems pharmacology approach is presented for illustrating the molecular correlations between pungent flavored compounds and their holistic efficacy at the special organ level. First, we identified target proteins that are associated with pungent flavored compounds and found that these targets were functionally related to CVDs and liver diseases. Then, based on the phenotype that directly links human genes to the body parts they affect, we clustered target modules associated with pungent flavored compounds into liver and heart organs. We applied systems-based analysis to introduce a pungent flavored compound-target-pathway-organ network that clarifies mechanisms of pungent substances treating cardiovascular diseases and liver diseases by acting on the heart/liver organ. The systems pharmacology also suggests a novel systematic strategy for rational drug development from pungent TCMs in treating cardiovascular disease and associated liver diseases.

Keywords: TCM; pungent flavored compound; cardiovascular disease; liver disease; systems pharmacology; blood-activating and stasis-resolving; organ location

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, with ischemic heart disease, heart failure, and stroke accounting for the majority of deaths [1–4]. Cardiovascular disease progresses by biological processes in the arteries and heart that eventuate in myocardial infarction, stroke, heart failure, and other vascular morbid events [2,3].

Vegetarian dietary patterns reduce CVD mortality and the risk of coronary heart disease (CHD) by 40% [1]. Plant-based diets are the only dietary pattern to have shown a reversal of CHD [1]. Traditional Chinese medicines (TCMs) are natural source herbal medicines, and Chinese ancient medical practitioners gradually comprehended the influence that TCMs (several plants and animals) exerted on the human body during the long-term practice. TCM plays an important role in the treatment of cardiovascular diseases.

Modern pathology shows that blood stasis is generally manifested by cardio-cerebrovascular diseases, such as myocardial infarction, coronary heart disease, and high blood pressure, resulting from hematological disorders including hemorrhage, congestion, thrombosis, and local ischemia [5,6]. Blood-activating and stasis-resolving (BASR) TCMs are mainly used to treat blood stasis syndrome. They have been widely applied in treating cardiovascular disease [7–10] in modern science. BASR herbs [11–13] are mainly include *Chuanxiong Rhizome* (Chinese name Chuanxiong), *Carthami Flos* (Chinese name HongHua), *Radix Salviae* (Chinese name DanShen), *Radix Paeoniae Rubra* (Chinese name ChiShao), *Curcumaelongae Rhizoma* (Chinese name JiangHuang), *Dalbergiae Odoriferae Lignum* (Chinese name JiangXiang), *Foeniculi Fructus* (Chinese name XiaoHuiXiang), *Angelicae Sinensis Radix* (Chinese name DangGui), and *Panax Notoginseng* (*Burk.*) *F. H. Chen Ex C. Chow* (Chinese name SanQi), etc. These BASR TCMs mainly exert therapeutic effects by improving cardiovascular activities [14,15]. They also have been widely applied routinely in clinical practice for treating coronary heart disease [10,12,15,16], cardio protection [17–19], anginapectoris [20,21], hypertension [22], and hyperlipidemia [23], etc.

Chronic liver disease (CLD) is a major cause of mortality, morbidity, and health care resource utilization worldwide [24]. From 1980 through 2010, mortality related to CLD increased by 46% worldwide [25]. WHO estimates that liver cancer is responsible for around 47,000 deaths per year in Europe. Liver disease affects young and middle-aged people, and in terms of years of life lost (YLL), liver cirrhosis is the 13th leading cause globally, the sixth leading cause of YLL in the developed world, and the eighth leading cause in Western Europe [25]. The incidence and prevalence of cirrhosis and primary liver cancer are key to understand the burden of liver disease [26].

Harmful alcohol consumption, viral hepatitis B and C, and metabolic syndromes related to overweight and obesity are the leading causes of cirrhosis and primary liver cancer in Europe [27]. Available data suggest the prevalence rate of non-alcoholic fatty liver disease (NAFLD) is 2 to 44% in the general European population (including obese children) and 42.6 to 69.5% in people with type 2 diabetes [27]. The hospitalized cases and mortality from alcoholic liver disease (ALD) are increasing in Taiwan and worldwide. Meanwhile, the Asia Pacific region also has a high prevalence of hepatitis B virus (HBV) and hepatocellular carcinoma (HCC) [27]. Chronic hepatitis B affects 0.5 to 0.7% of the European population. In the last decade, the prevalence of chronic hepatitis C was 0.13 to 3.26% [27].

Non-alcoholic fatty liver disease and nonalcoholic steatohepatitis can lead to advanced liver disease [28]. NAFLD is a common cause of chronic liver disease, and its worldwide prevalence continues to increase with the growing obesity epidemic [29].

Non-alcoholic steatohepatitis (NASH) has a potentially progressive course leading to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC), and liver transplantation [30,31]. The global epidemic of obesity has been accompanied by a rising burden of NAFLD, with manifestations ranging from simple steatosis to non-alcoholic steatohepatitis, potentially developing into hepatocellular carcinoma [32]. NAFLD is a leading cause of end-stage liver disease, hepatocellular carcinoma, and liver transplantation worldwide [33–36]. The prevalence of NAFLD is increasing at approximately the same rate as obesity. NASH and most importantly, fibrosis severity have been strongly implicated in the long-term prognosis of NAFLD patients [37–40].

To make traditional Chinese medicine (TCM) serve people all over the world better and accelerate the promising TCM-based new drug development, it is necessary to bring the ancient practice of (TCM) into line with modern standards world [41–46], among which the elucidation of the molecular mechanisms of TCM is one of the most important issues. Specifically, the material basis and the molecular mechanism of pungent flavor is not yet clear.

In our recent research, we found that the pungent TCMs have the vastness of spices. Moreover, we would elucidate the material basis of pungent flavor based on the spicy compounds and the molecular mechanism of pungent flavor based on the transient receptor potential (TRP) cation channel family (Figure 1). The pungent flavor profiles of pungent TCMs always have a fragrant smell and pungent taste (Table 1). Each pungent TCM contains at least one spice or pungent flavored compound. Spices are defined as any dried, fragrant, aromatic vegetable or plant substance that contributes flavor in a whole,

broken, or ground form with a strong taste [47,48]. Spices also have been used for thousands of years to enhance the flavor, color, and aroma of food [9]. In addition, they are known for their preservative and medicinal value [49,50]. In the past three decades, it has been experimentally documented that several common spices can also exert beneficial health physiological effects [51]. The antioxidant properties of herbs and spices are of particular interest given the impact of oxidative modification of low-density lipoprotein cholesterol in the development of atherosclerosis [52]. Consumption of garlic or garlic oil has been associated with a reduction in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels [52]. Studies suggest that an intake of between half and one garlic clove per day can reduce cholesterol by 9% [53,54].
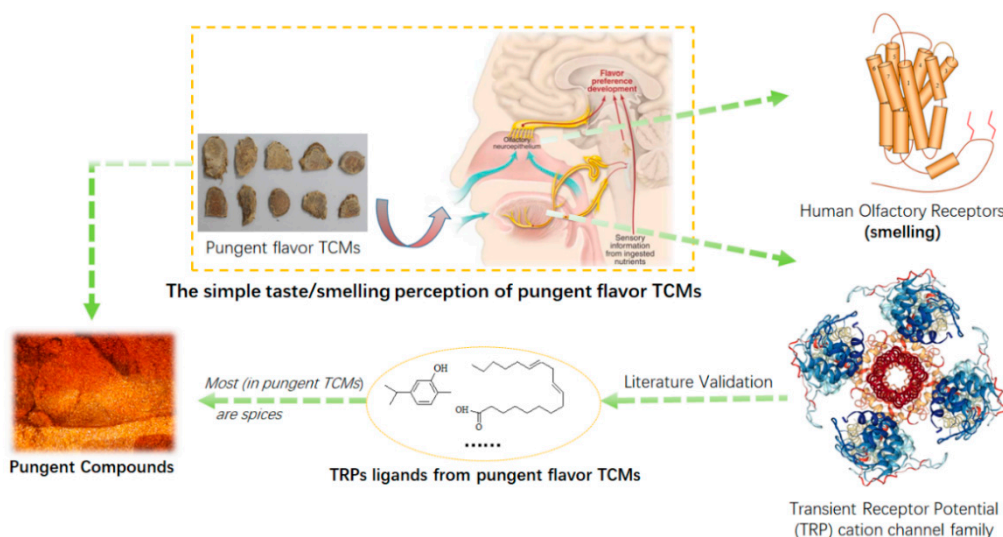
Figure 1. Process of discovering the pungent flavored materials from traditional Chinese medicines (TCMs).

Table 1. The flavor of some pungent traditional Chinese medicines (TCMs).

Latin Name	English Name	Chinese Name	Flavor
Piper Nigrum	Black pepper	Heihujiao	Fragrant smelling, taste pungent
Syzygium aromaticum	Cloves	Dingxiang	Strong fragrant smelling, taste pungent and feeling on tongue
Trigonella foenum-graecum L.	Fenugreek	Huluba	Sweet smelling aroma; fragrant
Menthae Haplocalycis Herba	Peppermint	Bohe	Cool and fragrant smelling, taste pungent
Zanthoxyli Pericarpium	Pepper	Huajiao	Fragrant smelling; taste sweet and pungent
Myristicae Semen	Nutmeg	Roudoukou	Strong fragrant smelling, taste pungent
Aucklandiae Radix	Common vladimiria root	Muxiang	Specific fragrant smelling, taste slightly bitter
Origanum vulgare L.	Oregano	Niuzhi	Taste pungent and slightly bitter
Thymus mongolicusRonn	Thyme	Bailixiang	Taste pungent
Cinnamomt Cortex	Cinnamon	Rougui	Strong fragrant smelling, taste sweet and pungent
Rosmarinus officinalis	Rosemary	Midiexiang	Pungent
Allii Sativi Bulbus	Garlic	Dasuan	Specific smelling, taste pungent
Zingiberis Rhizoma Recens	Ginger	Shengjiang	Specific fragrant smelling, taste pungent
Alpiniae Officinarum Rhizoma	Galangal	Gaoliangjiang	Fragrant smelling, taste pungent

In worldwide studies, spices have been linked to the prevention and treatment of chronic conditions such as heart disease, cancer, Type II diabetes, and Alzheimer's [9]. Spices are described as possessing medicinal properties, such as being anti-oxidant, antibacterial, antithrombotic, anti-atherosclerotic, hypolipidemic, hypoglycemic, anti-inflammatory, and antiarthritic, etc. [50–55]. The Spices have always been used as medicine because they are natural products easily absorbed by our bodies and generally do not have any adverse effects [49,56].

Herbal remedies are an important source for the discovery of new antibiotics and numerous studies have identified compounds within herbal plants that are effective [49,57–59]. Specifically,

the pungent TCMs have numerous spices that have a great potential to be developed as new and safe agents.

Spices in food and beverages and compounds in tobacco smoke interact with sensory irritant receptors of the transient receptor potential (TRP) cation channel family [60]. The TRP channels are polymodal transducers accepting a multiplicity of exogenous and endogenous chemicals as agonists [61–63]. This pungency is attributable to chemicals that activate a specific ion-channel protein, known as transient receptor potential ankyrin 1 (*TRPA1*) [64–67]. *TRPV1* (vanilloid type 1), *TRPA1* and TRPM8 (metastatic 8) not only elicit action potential signaling through trigeminal nerves, eventually evoking pungent or cooling sensations, but by their calcium conductance, they also stimulate the release of calcitonin gene-related peptide (CGRP) [60]. Moreover, *TRPA1* channels are activated by pungent compounds found in garlic, onion, mustard, and cinnamon extracts [68].

In the research field of pungent flavor in TCM terms, the ligands of TRPs ion channels have potential efficacy in cardiovascular diseases. For example, Capsaicin (highly pungent, highly volatile with a pungent odor) is a naturally occurring compound found in many pungent TCMs (*Alpiniae Officinarum Rhizoma*, *Capsici Fructus*, *Bupleuri Radix*, *Ginkgo Nut*), and it can activate the TRPV1 ion channel [69]. Eugenol (Spicy, pungent taste) is a colorless to pale yellow, aromatic oily liquid extracted from some pungent TCMs (*Cinnamomi Ramulus*, *Caryophylli Flos*, *Zingiber Rhizoma Recens*), and it can activate *TRPV1* [70,71], *TRPM8* [71], *TRPA1* [71], and *TRPV3* [72–74]. Carvacrol (characteristic pungent, warm odor) is a natural aromatic hydrocarbon that occurs in many pungent TCMs (*Angelicae Sinensis Radix*, *Carthami Flos*, *Moslae Herba*), and it can activate *TRPA1* [75,76], TRPM7 [77], *TRPV3* [73].

To clarify molecular mechanisms of pungent flavor for complex related diseases from a system level, the following numerous issues need to be solved urgently: (1) Which compounds are the material base of the pungent flavor in the pungent TCMs? (2) And how the pungent flavored compounds from pungent TCMs act on the heart heart/liver to treat CVDs and liver diseases clinically? (3) Which pungent flavored compounds are involved in the regulatory processes of the formulae in CVDs and liver diseases? (4) Which targets are modulated by the pungent flavored compounds to achieve the therapeutic effect? (5) Which pathologic processes are regulated by the pungent flavored compounds and herbal medicine to treat CVDs and liver diseases simultaneously? (6) Whether the pungent flavored compounds could treat CVDs and liver diseases simultaneously? In this research, the pungent flavored compounds' holistic efficacy was mapped into the liver/heart organ by the pungent flavored compound targets. How the pungent flavored compounds from BASR TCMs treat CVDs and liver diseases by acting on the liver /heart organ is explained. The function of pungent flavor in pungent TCM is not so easily understood, and many further studies need to be considered for drug development based on the function of pungent flavor in TCM.

2. Results

2.1. Collecting the Compounds of Pungent TCMs

We collected 1159 compounds of pungent TCMs (see Table 2 for further details) and identified 39 pungent flavor compounds (see Table 3 for further details of pungent compounds).

Table 2. Data sets on pungent compounds to evaluate structure clustering.

Latin Name	Chinese Herb	Diversity	No. Entries	Descriptor
Chuanxiong Rhizome	ChuanXiong	0.6678	352	
Carthami Flos	HongHua	0.7011	272	TCMID, TCMSP,
Dalbergiae Odoriferae Lignum	JiangXiang	0.5255	169	BATMAN-TCM, TCM Database@Taiwan,
Foeniculi Fructus	XiaoHuiXiang	0.6495	74	TCM-Mesh
Angelicae Sinensis Radix	DangGui	0.7116	292	

Table 3. Pungent flavored compounds from pungent TCMs.

Latin Name	Herbs	Molecule Name	FEMA or PubChem ID
Chuanxiong Rhizome	ChuanXiong	Ethylpalmitate	2451
		Trimethylamine	3241
		Vanillin	3107
		Nonanal	2782
		1,8-cineole	2465
		Myrcene	2762
		Methyleugenol	2475
		hexanal	2557
		thymol	3066
		trans-2-Nonen-1-ol	3379
		P-Cymene	2356
		Borneol	2157
		Naphthalene	pubchem_931
		Phenylacetaldehyde	2874
		O-Cresol	3480
		Linalool	2635
		Camphene	2229
		Linoleic Acid	3380
		3-Carene	3821
Angelicae Sinensis Radix	DangGui	2-pentylfuran	3317
		Camphene	2229
		Carvacrol	2245
		o-Cresol	3480
		p-Cresol	2337
		p-Ethylphenol	3156
		Guaiacol	2532
		Isoeugenol	2468
		Phenol	3223
		Vanillin	3107
		Nonanal	2782
		Myrcene	2762
		naphthalene	pubchem_931
		1-hexadecanol	2554
		m-cresol	3530
		3-carene	3821
		Benzothiazole	3256
		3-Hexanol	3351
Carthami Flos	HongHua	Phenylacetaldehyde	2874
		Nonanal	2782
		Methylcinnamate	2698
		carvacrol	2245
		Isovalericacid	3102
		stearicacid	3035
Dalbergiae Odoriferae Lignum	JiangXiang	1,8-cineole	2465
		indole	2593
		Ethylpalmitate	2451
		D-Limonene	2633
		α-Terpinene	3558
Foeniculi Fructus	XiaoHuiXiang	Terpinolene	3046
		1,8-cineole	2465
		Myrcene	2762
		acetaldehyde	2003
		d-fenchone	2479

2.2. Pungent Flavor Compound-Target Network

In the pungent flavor compound-target network, *NFE2L2* (Nuclear factor erythroid 2-related factor 2) was the target with the highest degree (DD = 16), followed by AR (Androgen Receptor, DD = 15), *PTGS2* (Prostaglandin G/H synthase 2, DD = 13), *TNF* (Tumor necrosis factor, DD = 13), *NFKB1* (Nuclear factor NF-kappa-B p105 subunit, DD = 12), PPARD (Peroxisome proliferator-activated receptor delta, DD = 12), *CYP1A1* (Cytochrome P450 1A1, DD = 12), *JUN* (Proto-oncogene c-JUN, DD = 11) and etc.

Evidence suggests that the pungent flavored compounds in pungent TCMs can act on these targets, thus, contributing to the therapeutic effect on cardiovascular diseases and liver diseases. For example (as shown in Table 4), (1). *NFE2L2* mediates activity in several organs, including those in the kidney. The transcription factor Nrf2, encoded by *NFE2L2* gene is a key regulator of cellular defense

against oxidative and electrophilic stress, also governing the expression of many phase II detoxification enzymes [78]. Nrf2 is mainly expressed in hepatocytes [79] and could protect against ethanol-induced liver injury [80]. *NFE2L2* is an important component in antioxidant defenses in cardiovascular diseases such as atherosclerosis [81–83], hypertension [84–87], and heart failure [88–91]. Moreover, *NFE2L2* is important to vascular integrity and long-term endothelial function, for example, sustained release of NO and protection from apoptosis [92–96]. Laminar blood flow promotes antiatherogenic activation of *NFE2L2*, and oscillatory blood flow suppresses *NFE2L2* activation, creating a proatherogenic environment [94,97]. Nrf2 is also an important factor in the modulation of response to oxidative stress and inflammation, and both processes playing a role in liver fibrogenesis [78,98,99]. Expression levels of Nrf2 may be decreased in end-stage liver disease [78]. Additionally, there have not been clinical trials on the effects of Nrf2 activation on liver injury and disease [100,101].

Table 4. TOP 20 Targets information of pungent TCMs in the cardiovascular system.

Target	UniProt ID	Gene Name	Related Diseases	Degree
NFE2L2	Q16236	Nuclear factor erythroid 2-related factor 2	Atherosclerosis, hypertension, Heart failure	16
AR	P10275	Androgen Receptor	Atherosclerosis, Coronary artery disease, Hypertension, Myocardial infarction	15
PTGS2	P35354	Prostaglandin G/H synthase 2	Pain, Coronary heart disease, Myocardial infarction, Vascular lesion regression	13
TNF	P01375	Tumor necrosis factor	Heart failure, Hepatitis C infection, Hypertension, Coronary atherosclerosis, Cirrhosis	13
NFKB1	P19838	Nuclear factor NF-kappa-B p105 subunit	Atherosclerosis, Cancer, Type 2 diabetes, Hepatitis C, Chronic Liver cirrhosis	12
PPARD	Q03181	Peroxisome proliferator-activated receptor delta	Central nervous system disease, Metabolic disorders, Atherosclerosis, Coronary; Coronary heart disease	12
CYP1A1	P04798	Cytochrome P450 1A1	Liver cancer; Liver disease, Coronary artery disease, Hypertension	12
JUN	P05412	Proto-oncogene c-JUN	Heart failure, Breast cancer	11
CYP2E1	P05181	Cytochrome P450 2E1	Liver cancer; Liver disease	10
AHR	P35869	Aryl hydrocarbon receptor	Multiple myeloma, HIV infections, Myocardial infarction	10
CAT	P04040	Catalase	Skin burns, Heart failure	10
ALB	P02768	Serum albumin	Hemophilia' Visualizing lesions with abnormal blood brain barrier	10
PTGS1	P23219	Cyclooxygenase-1	Platelet function, Myocardial Infarction, Acute coronary syndrome	9
CXCL8	P10145	Interleukin-8	Melanoma. Autoimmune diabetes	9
MMP9	P14780	Matrix metalloproteinase 9	Atherosclerosis, Carotid, Colorectal cancer	9
HMOX1	P09601	Heme oxygenase 1	Myocardial infarction, Atherosclerosis, Coronary, Cardiovascular disease, Ischemic injury of the liver, Inflammation, Cerebral vasospasm	9
IL1B	P01584	Interleukin-1 β	Coronary disease, Hypertension, Chronic hepatitis C	8
IL6	P05231	Interleukin-6	Arteriosclerosis, Heart valve diseases, Hepatitis B	8
ACE	P22303	Acetylcholinesterase	Chronic heart failure, Hypertension	8
HSPB1	P04792	Heat shock protein β-1	Breast cancer. Ovarian cancer, Bladder cancer, Prostate cancer, Lung cancer, Arthritis	8

(2) Androgen receptor (*NR3C4*, or AR) is another important steroid hormone receptor that is activated by endogenous androgens, mainly testosterone and 5α- dihydrotestosterone (5α-DHT). The androgen receptor (AR), also known as *NR3C4* (nuclear receptor subfamily 3, group C, member 4), is a ligand-dependent transcription factor (TF) belonging to the steroid hormone receptor (SR) group of the nuclear receptor (NR) superfamily. In humans, this superfamily contains 48 NRs. The human AR gene is located on the X chromosome [102–104]. As a sex hormone receptor, AR mediates the physiological actions of androgen, which is responsible for male sexual differentiation and pubertal changes. Accordingly, AR is mainly expressed in androgen target tissues, such as the reproductive tissues (i.e., prostate, seminal vesicle, epididymis, and testes), skeletal muscle, liver [105,106], and central nervous system (CNS) [107]. Androgens play a role in inducing vascular calcification through

the AR [108]. ARs have illustrated clinical consequences that further explain the conflicting data on male hypogonadism and cardiovascular disease [109,110].

(3) Cytochrome P450 1A1 (*CYP1A1*), The cytochrome P450 (CYP) monooxygenase system is a superfamily of enzymes, which play a central role in the etoxication and metabolic activation of xenobiotics [111,112]. The highest expressions of CYP 450 are generally found in liver tissue [113], but the distribution of particular CYPs varies [114], which indicates that the actual efficiency of a drug is likely to depend on CYP expression in the target tissue. *CYP1A1* is one of the most important enzymes implicated in the metabolic activation of carcinogens. Cytochrome P450 enzymes could also express in the heart and could have an important role in the metabolism of endogenous compounds [115]. *CYP1A1* could protect against NAFLD pathogenesis [80,81,116,117]. *CYP1A1* and *CYP1A2* also play a protective role in liver damage caused by 2, 3, 7, 8-tetracholorodibenzo-p-dioxin (TCDD) and bile duct ligation (BDL) [118]. Many findings indicated that the small compounds could enhance hepatic cytochrome P450 1A1 mRNA expression in liver in animals [119–125]. Many researches have also shown that enzymatically functional *CYP1A1* appears to be expressed in human livers [126–128].

To decipher the action mechanism of 81 targets associated with the cardiovascular system, ClueGO, a widely used Cytoscape plugin, was applied to identify biological interpretation and interrelations of functional groups in biological networks [126–128]. ClueGO creates, first, a binary gene-term matrix with the selected terms and their associated genes. Based on this matrix, a term–term similarity matrix is calculated using chance-corrected kappa statistics to determine the association strength between the terms [129]. The size of the nodes reflects the enrichment significance of the terms. As shown in Figure 2, the results were divided into three stratums: molecular functions; the reactome analysis, and biological process. Specially, the molecular functions mainly consisted of five groups: (1) heme binding; (2) RNA polymerase II transcription factor activity, ligand-activated sequence-specific DNA binding; (3) phosphatase binding; (4) RNA polymerase II transcription factor binding, and (5) MAP kinase activity, which indicated that most potential targets were related to heme binding and MAP kinase activity (Figure 2A). The reactome of the targets were mainly related to MEOS oxidizing ethanol to acetaldehyde, *c-FOS* activation phosphor *ERK1/2*, *TP53* and *AP-1* bind the *MSH2* promoter, Expression of *IL4*, *IL3*-downregulated extracellular genes, express of *PPARG* (Figure 2B). These biological functions have been linked to response to lipid, cellular response to lipid, blood circulation, circulatory system process, negative regulation of the apoptotic process (Figure 2C). Finally, we found that most of the targets were related to the activation of MAP kinase, heme binding and regulation of inflammatory factors.

2.3. Organ Targets Location Map

We applied systems-based analysis to introduce a compound-target-pathway-organ network that elucidated the pungent flavored compounds' holistic efficacy at special organ level and mechanisms of pungent flavored compounds effect in treating cardiovascular diseases and liver diseases. To further explore the underlying mechanisms of pungent flavored compounds that provide therapeutic effects in CVDs and liver diseases, we studied the organ target location based on tissue expression profile and phenotypic effects.

We enriched the overrepresented gene ontology (GO) terms and checked the tissue distribution of the obtained targets. For GO analysis, the biological process of GO vocabulary (GOBP) was identified through GOBP terms by the DAVID database (https://david.ncifcrf.gov/) [130], and GOBP terms with adjusted *p*-values < 0.001 were observed. The target tissue distribution was determined based on the microarray analyses data of different tissue types lodged in the BioGPS bank (accessible at http://biogps.org) [131,132]. Subsequently, we mapped these 117 targets related to the cardiovascular system into the DAVID database (https://david.ncifcrf.gov/) [130] to identify the significant tissues location. The tissues location map (Figure 3) showed that 31.6% of the targets contain higher mRNA expression in liver tissue than other tissues.
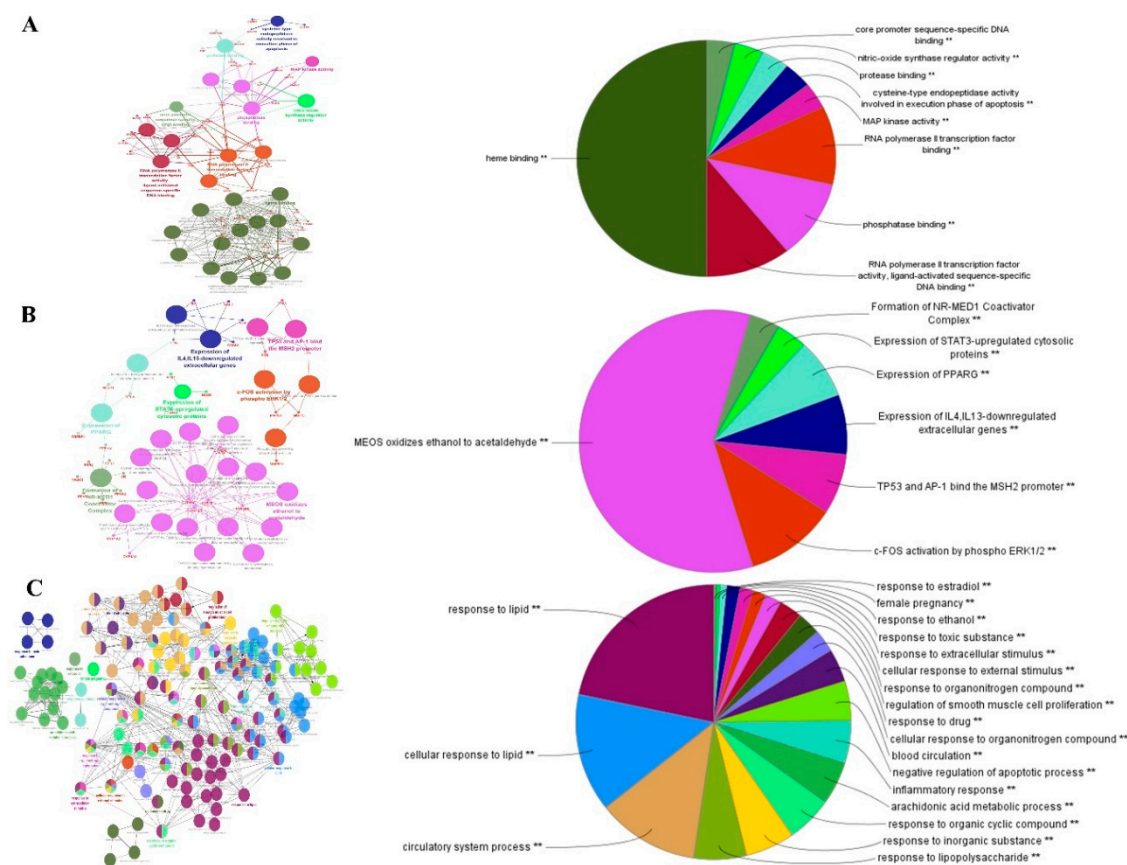
Figure 2. ClueGO analysis of the pungent flavored compound targets. A functionally grouped network of enriched categories was generated for the target genes. Gene ontology (GO) terms are represented as nodes, and the node size represents the term enrichment significance. Functionally related groups partially overlap. The node pie charts represent the molecular function, immune system processes, reactome analysis of targets. Only the most significant term in the group was labeled. (**A**) Representative molecular function interactions among targets. (**B**) Representative reactome analysis interactions among pungent flavored compounds' targets. (**C**) Representative biological process among pungent flavored compounds' targets.
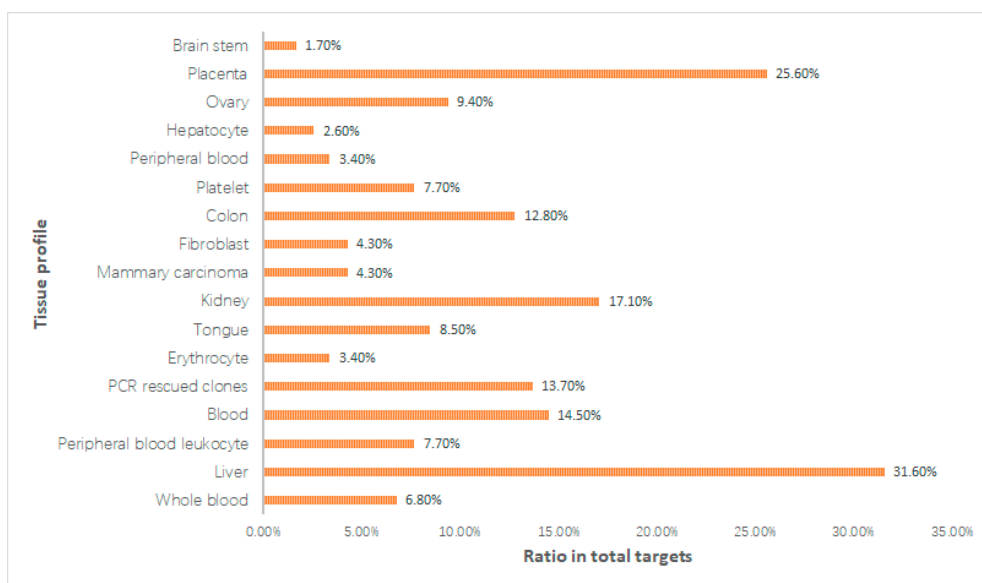
Figure 3. The target tissue distribution based on tissue expression profile.

To understand how the multi-organs respond to indications may facilitate the development of enhanced detection and treatment modalities for complex disease on a system level, the target organ location map was constructed (Figure 4). As shown in Figure 4, 59 shared targets of the liver and heart organ were identified. Therefore, shared targets of the heart and liver could provide novel target potential for the treatment of CVDs and liver diseases. If two diseases share a large number of disease genes, the disease pairs become more comorbid, and they are closely associated [133].
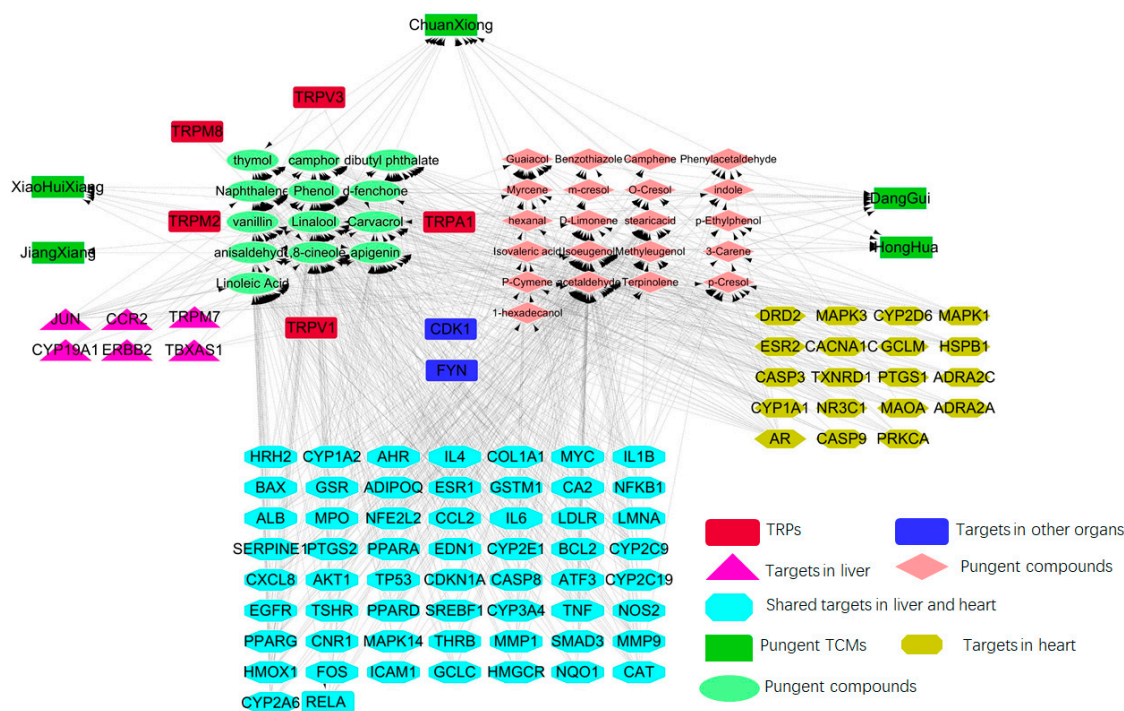
Figure 4. Target organ location map. The green diamond represents 5 pungent TCMs, and purple–red node represents the pungent flavored compounds. The pink triangle, yellow-green hexagon represents the target nodes along with the organs (Liver, heart) in which the target is located. The cyan ellipse represents the shared targets in liver and heart.

Eighty-one targets related to cardiovascular system were mapped into 125 organs at different levels according to the Gene ORGANizer database (accessible at http://geneorganizer.huji.ac.il/) [134]. Gene ORGANizer is a phenotype-based tool that directly links human genes to the body parts they affect, and it provides partial or skewed information on the whole organs. Gene ORGANizer can analyze gene lists to test whether they are enriched. Thus, Gene ORGANizer is a tool that enables researchers to analyze associations with organs in a genome-wide context. Third, Gene ORGANizer focuses on whole organs (e.g., heart), systems (e.g., the cardiovascular), or anatomical regions (e.g., the thorax), rather than on specific cell types or tissues (e.g., cardiomyocytes) based on expression analyses [134]. This research explored the potential mechanism of pungent flavored compounds in the treatment of cardiovascular diseases and liver diseases. More importantly, we compared the organ patterns based on the distribution of pungent flavored compound targets in the heart and liver. Based on the target phenotype pattern, the organ targets location map was divided into two organ modules, namely liver organ and heart organ. The organ distribution of 81 pungent flavored compound targets in cardiovascular system is shown in Figure 4.

Therefore, these 62 liver high-abundant targets are considered as the liver organ, accounting for 76.5% of 81 targets related cardiovascular system. There are 77 targets (accounting for 95.1% of 81 targets related cardiovascular system) located in the heart, they are potentially effective targets for the treatment of CVDs. In addition, there are 59 targets shared between liver organ and heart organ.

Most targets acted on both liver organ and heart organ, which suggests that the two organs are closely correlated. Forty-one targets were involved in the most highly related pathways associated with CVDs and liver diseases, which may provide a basis for CVDs and liver diseases treatment strategies as well.

2.4. Target-Pathway Network

In this section, pathways directly related to CVDs were assembled into a "CVDs pathway" based on the present cognition of CVDs pathology. The mechanisms of pungent flavored compounds treating liver diseases were mapped to the Target-Pathway (T-P) network according to their target's information. The T-P network could elucidate the function of potential target proteins related to CVDs [135] and liver diseases [136] in the KEGG (Kyoto Encyclopedia of Genes and Genomes) biological pathway. To understand the molecular mechanisms of pungent flavor and liver/heart organ in treating cardiovascular diseases and liver diseases, we mapped the targets onto their related pathways extracted from the KEGG database (www.genome.jp/kegg) [137] and generated a bipartite graph of T-P Network (Figures 5 and 6), in which a compound and a signal pathway were linked if the compound targets on the proteins appeared in the signal pathways.
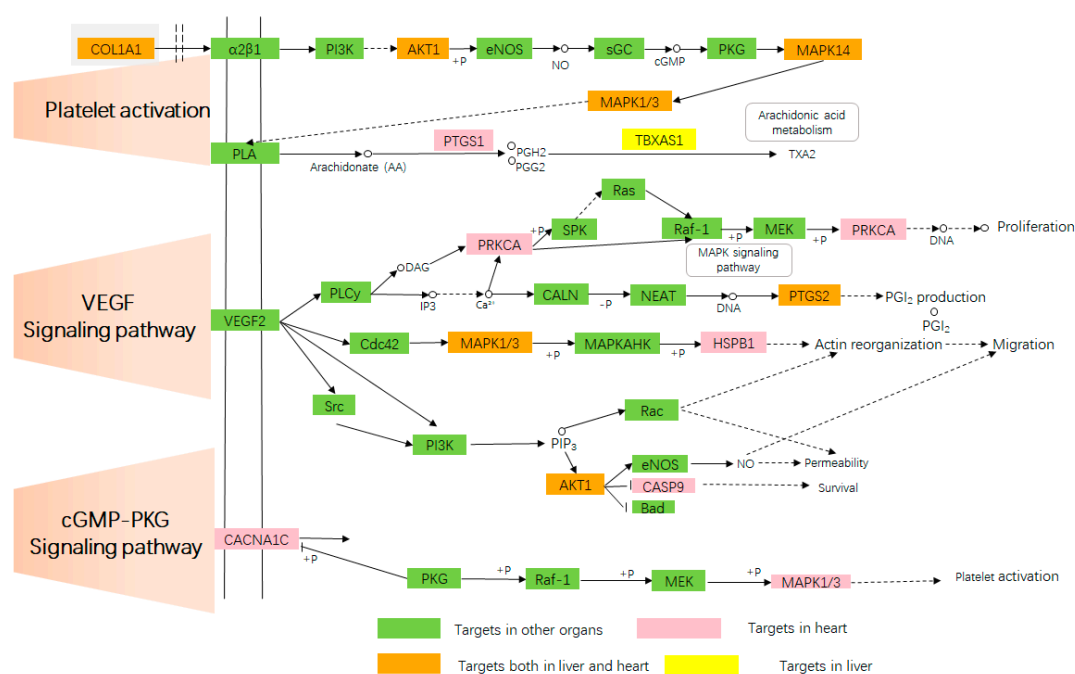
Figure 5. The representative cardiovascular disease pathway. The solid arrow represents molecular interaction or relation (activation), the dashed arrows indirect link or unknown reaction. The circle represents chemical compound, DNA and other moleculee. ⊣: molecular interaction or relation (inhibition). ⟶ : Phosphorylation, ⟶ : dephosphorylation.

Similarly, major pathways (111/121) are also modulated with adjusted *p*-values < 0.05, and many of them have been proved as suitable therapeutic pathways for CVDs and liver diseases, such as cGMP-PKG (cyclic guanosine monophosphate-dependent protein kinase) signaling pathway (hsa04022), VEGF (vascular endothelial growth factor) signaling pathway (hsa04370), Platelet activation (hsa04611), NAFLD (hsa04022), Hepatitis B (hsa05161), Hepatitis C (hsa05160), Hepatocellular carcinoma (hsa05225), and drug metabolism–cytochrome P450 (hsa00982). The cGMP-PKG signaling pathway plays a significant role in cardio protection by monitoring cell death and maintaining intracellular acidosis [138]. The cGMP/PKG signaling pathways are involved in platelet inhibition [139]. The cGMP-PKG signaling pathway was first described to unfold vascular effects by mediating smooth muscle relaxation [140] but was then also linked to beneficial

myocardial effects by attenuating hypertrophy and pathological remodeling [141]. Platelets play an important role in hemostasis and clot formation [142]. Platelets are involved in the early phases of liver regeneration [143]. Platelet activation is a complex process that involves different cellular signaling pathways [144]. Platelets play a key role in many physiological functions especially in hemostasis and wound healing processes to maintain the integrity of the circulatory system [145,146]. Increased levels of oxidative stress contribute to the development of atherosclerosis that eventually leads to thrombosis; a principal cause of heart attacks and strokes [144]. The vascular endothelial growth factor (VEGF) signaling pathway (VSP) fulfills a cardinal role in endothelial cells, and its inhibition has a profound cardiovascular impact [147]. VSP inhibitors are used as anti-angiogenic therapies. Generalized endothelial dysfunction predisposes to vasoconstriction, atherosclerosis, platelet activation, and thrombosis (arterial more than venous) [147]. It is generally accepted that VEGF is a major driver of the angiogenic process in physiological and pathological processes in both embryo and adult [148,149]. NAFLD (hsa04022), Hepatitis B (hsa05161), Hepatitis C (hsa05160), Hepatocellular carcinoma (hsa05225) and Drug metabolism—cytochrome P450 (hsa00982) been shown to be highly relevant to liver diseases. These results illustrated pungent flavored compounds could treat cardiovascular diseases and liver diseases by acting on the heart/liver organ from the level of the biological pathway.
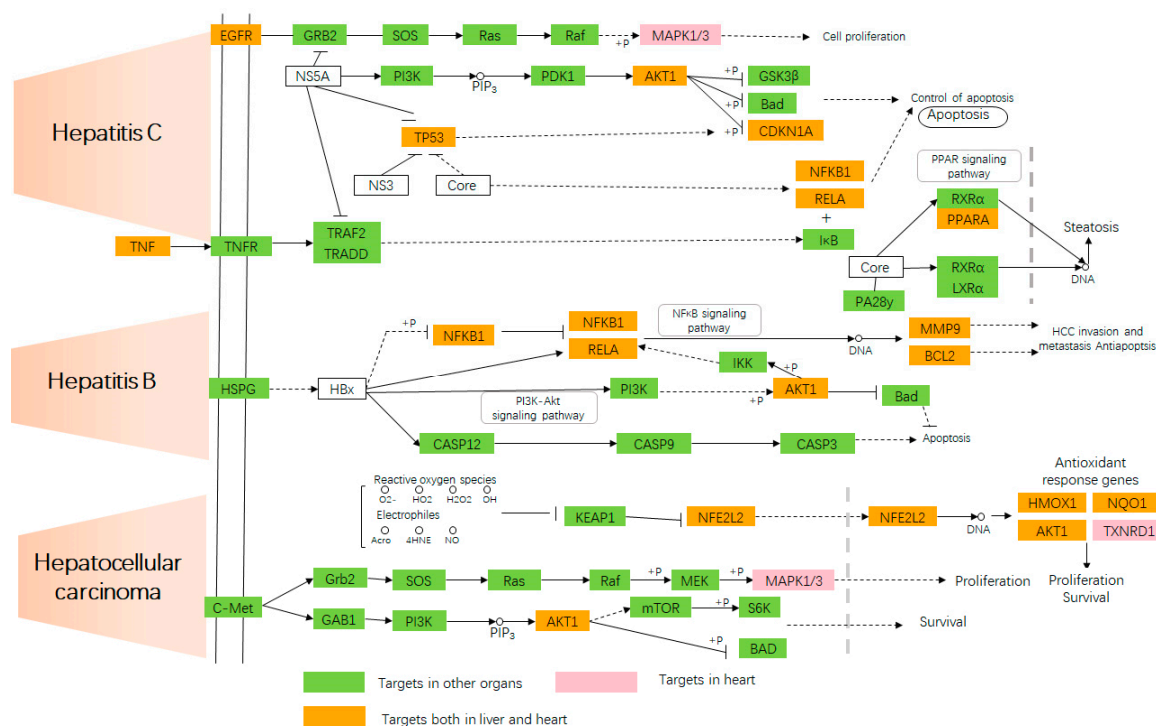
Figure 6. The representative liver disease pathway. The solid arrow represents molecular interaction or relation (activation), the dashed arrows indirect link or unknown reaction. The circle represents chemical compound, DNA and other moleculee. ⎯⎯⎯⏊: molecular interaction or relation (inhibition). ⎯⎯⎯▶: Phosphorylation, ⎯⎯⎯▶ : dephosphorylation.

3. Discussion

3.1. The Material Base of Pungent Flavor of Pungent TCMs

We first proposed that spice compounds from TCMs were considered as the material base of pungent flavor with pungent taste or smell. Not only do humans use spices, but also animals could use spices by nature. A study reveals that tiny birds on the French island of Corsica may decorate nests with sweet-smelling herbs to create a pest-free environment [48]. The birds incorporate fragments of

10 or more fragrant plants including yarrow, lavender, mint, and lemon balm into their nests. Maybe they can naturally distinguish the spices with smell or taste.

Spices are always pleasing with their color, flavor or pungency. Spices have been used for thousands of years to enhance the flavor, color, and aroma of food [49]. In addition, they are known for their preservative and medicinal value [49,50,150]. In the past three decades, it has been experimentally documented that several common spices can also exert beneficial health physiological effects [51]. The antioxidant properties of herbs and spices are of particular interest given the impact of oxidative modification of low-density lipoprotein cholesterol in the development of atherosclerosis [52]. Consumption of garlic or garlic oil has been associated with a reduction in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels58. Studies suggest that an intake of between half and one garlic clove per day can reduce cholesterol by 9% [53,54].

3.2. Pungent Compounds Provide Support for the Treatment of Cardiovascular and Liver Diseases

Pungent traditional Chinese medicine provides abundant resources of pungent compounds with a fragrant smell and pungent taste. The authors believe that the pungent compounds with pungent taste or aromatic odor from pungent TCMs are the material base of pungent flavor in TCM terms, and they have the potential action of blood-activating and stasis-resolving. These compounds are from natural products and have good bioavailability and non-toxic effects. Moreover, the pungent compounds are associated with undesirable effects on the cardiovascular system and temperature. These compounds could become a potential drug resource in treating cardiovascular and liver diseases.

3.3. Expression of Meridian Tropism at Level of Tissue and Organ

These traditional Chinese medicines often exhibit high similarity in their TCM herbal properties (TCM-HPs). The classic concept of TCM-HPs defines four fundamental characters (cold, cool, warm, and hot), five fundamental flavors (salty, sour, bitter, sweet, and pungent), four toxic states (toxic, nontoxic, very toxic, and slightly toxic), 12 meridians (bladder, spleen, large intestine, stomach, small intestine, liver, lung, heart, kidney, gallbladder, xin bao or pericardium and san jiao) [11,151,152]. TCM-HP is the core of basic theory of TCM and is the high recapitulation of clinical practice from ancient physicians [11]. They described TCMs from multiple perspectives (character, flavor, toxic, meridian, etc.), but due to the limitation of the medical level at that time, the scientific connotation of TCMs could not be explained at the molecular level. TCM-HP also provides strong evidence to guide the clinical application of TCM. From the view of modern science, four fundamental characters reflect the characters of TCMs, five fundamental flavors reflect the properties of TCMs, and meridians reflect human body parts which the TCMs act on. The TCM entering one meridian or several meridians means the corresponding efficacy of such herb has obvious action towards this or these organs/meridians with no obvious or even no effect on other parts [11].

Traditional Chinese medicine believed that the cardiovascule was deficiency in the "root" and excessed in the "branch". Its "root" was on liver and its "branch" was on heart. In the long-term clinical practice, the theory of treating cardiovascular diseases from the liver was gradually developed. The theory stems from Huangdi Neijing (The Yellow Emperor's Inner Canon) [153]. In traditional Chinese Medicine, the human body is considered as a holistic being in which each organ or each specific physiological part is interrelated. Based on Huangdi Neijing (The Yellow Emperor's Inner Canon) [153], traditional Chinese medical practitioners diagnose and treat patients beneath the guidance of meridian theory, declaring that the liver and heart linked through some specific Jingluo (meridians) [154], and they have an interaction effect in terms of both physiological function and pathological basis. As for physiological function, the heart is able to control the blood and vessels and govern the mind [135], while the liver stores blood, controls conveyance and dispersion, dominates the tendons, has its outward manifestation in the nails, and opens into the eyes.

However, the relationships between five flavors (the true taste or smell) and meridian tropism are not explicit. Additionally, the underlying molecular mechanisms of pungent flavor and liver meridian tropism in treating CVDs and liver diseases are yet unclear.

These five TCMs are with common traditional Chinese medicine herbal properties (TCM-HPs), namely warm, pungent, and liver meridian tropism. They all have the single pungent flavor and belong to the same liver meridian tropism. We will focus on the relationship between pungent flavor and the liver meridian tropism at the molecular level in treating cardiovascular diseases and liver diseases.

4. Materials and Methods

4.1. Date Collection and Visualization

In this work, the available information of traditional Chinese medicine herbal property (TCM-HP) was extracted from pharmacopoeia of the People's Republic of China (2015) [155], which consists of 5608 different species of drugs in the texts, such as herbs, plant oils, and extracts.

In this study, the blood-activating and stasis-resolving (BASR) TCMs of *Chuanxiong Rhizome* (Chinese name Chuanxiong), *Carthami Flos* (Chinese name HongHua), *Dalbergiae Odoriferae Lignum* (Chinese name JiangXiang), *Foeniculi Fructus* (Chinese name XiaoHuiXiang), and *Angelicae Sinensis Radix* (Chinese name DangGui) were selected as the research object for pungent flavor. These five BASR TCMs have the single pungent flavor and belong to the same liver meridian tropism [11,54,151].

A systems pharmacology approach was used to depict pungent compounds in treating CVDs and liver diseases from the molecular to holistic level. Briefly, as shown in Figure 7, we collected the compounds of pungent TCMs from TCMSP [156], TCMID [45,46], BATMAN-TCM [157], TCM-Mesh [158], TCM Database@Taiwan [159]. All of these compounds collected were normalized to the canonical SMILES format [160]. Duplicates from different sources and compounds without structures were excluded. The PaDEL-Descriptor [161] was used to generate a set of MDL (Molecular Design Limited) 166-key fingerprints for each TCM compounds. The MDL 166-key fingerprint is also known as the "Molecular Access System (MACCS)" key in the literature and is a no hashed fingerprint consisting of 166 bits. The MDL 166-key fingerprint is one of the very few availabilities that offers a 1-1 mapping. These fingerprints were assembled into the fingerprint array.

The potential related targets of pungent flavor compounds were from drugbank [162,163], STITCH [164], ChEMBL [165], BindingDB [166,167]. The obtained targets were mapping into relevant databases to find out their corresponding pathways of CVDs and liver diseases. Furthermore, network construction, pathway enrichment analysis, tissue location, and organ location analysis were performed to illustrate the molecular mechanisms of pungent compounds treating CVDs and liver diseases holistically.

We collected 1159 compounds of 5 pungent TCMs (Table 5) and then generate a set of MDL 166-key fingerprints for each compounds' with PaDEL-Descriptor [161]. The 1159 compounds from 5 pungent TCMs could be mapped into two-dimensional space with the PCA (Principal Component Analysis) method while maintaining a lot of geometric structure (Figure 8).

Table 5. The details of 5 pungent TCMs in this research.

Latin Name	Chinese Herb	TCM-HPs
Chuanxiong Rhizome	ChuanXiong	Warm, pungent, liver, gallbladder, pericardium meridian tropism
Carthami Flus	HongHua	Warm, pungent, liver, heart meridian tropism
Dalbergiae Odoriferae Lignum	JiangXiang	Warm, pungent, liver, spleen meridian tropism
Foeniculi Fructus	XiaoHuiXiang	Warm, pungent, liver, kidney, spleen, stomach meridian tropism
Angelicae Sinensis Radix	DangGui	Warm, pungent, liver, heart, spleen meridian tropism
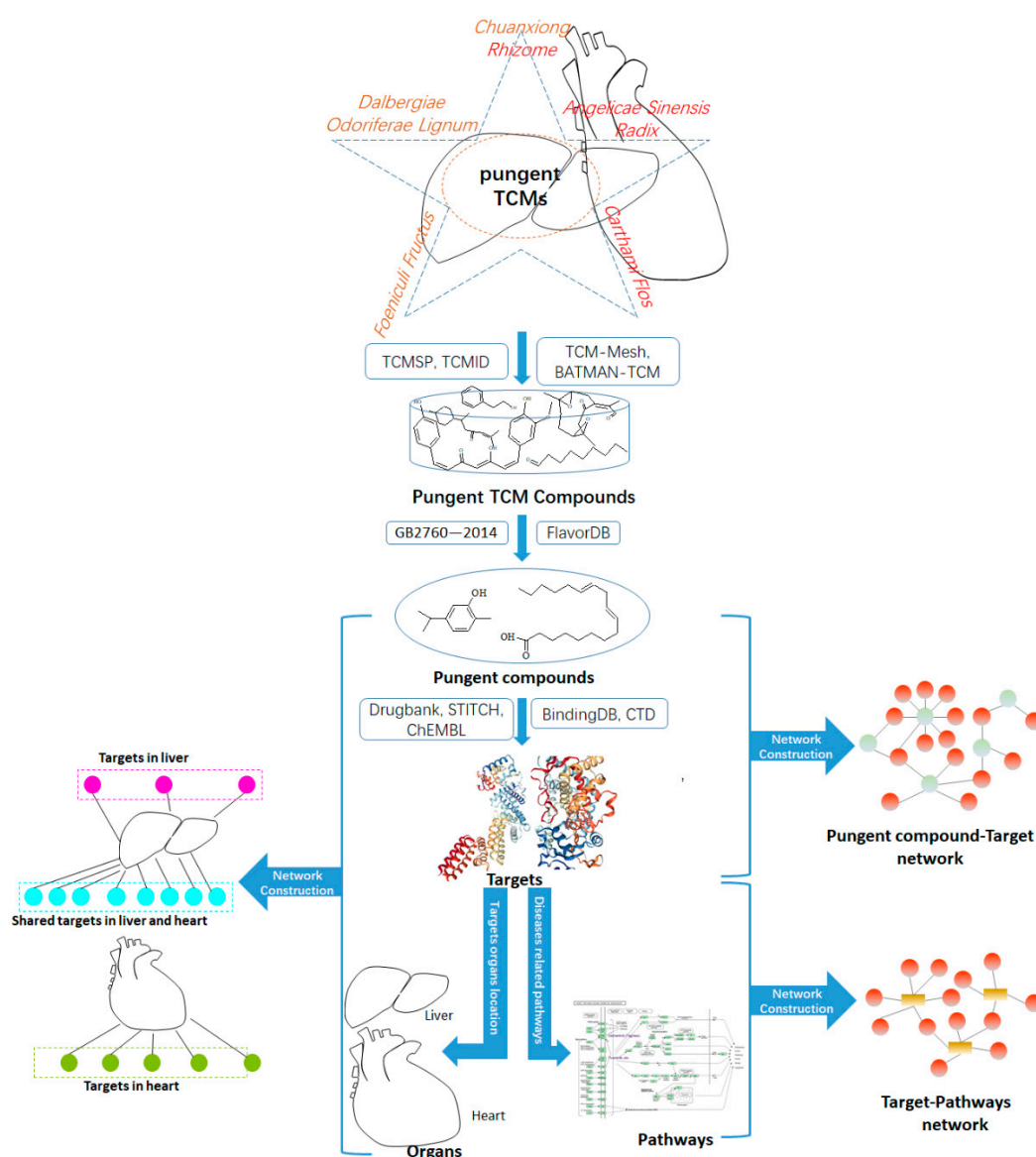
Figure 7. The workflow to study the relationship between pungent flavored compounds and their special targets organ location in the cardiovascular system. The cyan circle represents the shared target in liver and heart. The magenta circle represent the targets in liver. The yellowish green circle represents the target in heart.

It can be seen from Figure 8 that the structural formulae of these five pungent TCMs were similar, indicating that the five pungent TCMs have the same or similar efficacy. Nevertheless, there are many compounds with similar structure in these TCMs.

The pungent flavor compounds of pungent TCMs were identified from spice [168] with FEMA code [169] and flavorDB [170], which consisted of 1511 different spices and pungent flavor compounds in total.

The diversity of the pungent TCMs' compounds molecules within each TCM was computed as follows [171]. Let $d_{\mu\nu}$ be the Soergel-based [172] interdata set distance between the two TCMs' compounds sets D_μ and D_ν.

$$d_{\mu\nu} = \frac{1}{N_\mu N_\nu} \sum_{i=1}^{N_\mu} \sum_{j=1}^{N_\nu} d_{sg}\left(x_i^\mu, x_j^\nu\right) \tag{1}$$

where N_μ and N_ν are the number of molecules in TCM compound data set D_μ and D_ν, and x^s_γ is the fingerprint vector from row$\gamma$of the fingerprint array for data set D_s. Let d_μ be the diversity of the molecules within a single data set D_μ as Equation (1) [172].

$$d_{sg} \;=\; \frac{\sum_{k=1}^{d} |P_k - Q_k|}{\sum_{k=1}^{d} \max(P_k - Q_k)} \tag{2}$$

where P_k and Q_k are the fingerprint vector of two compounds in each pungent TCM compounds set.

The compounds data set of *Angelicae Sinensis Radix* (DangGui) has the greatest diversity (Table 2), so this data set is expected to exhibit the weakest clustering, and this pungent TCM has more extensive potential pharmacological effects.
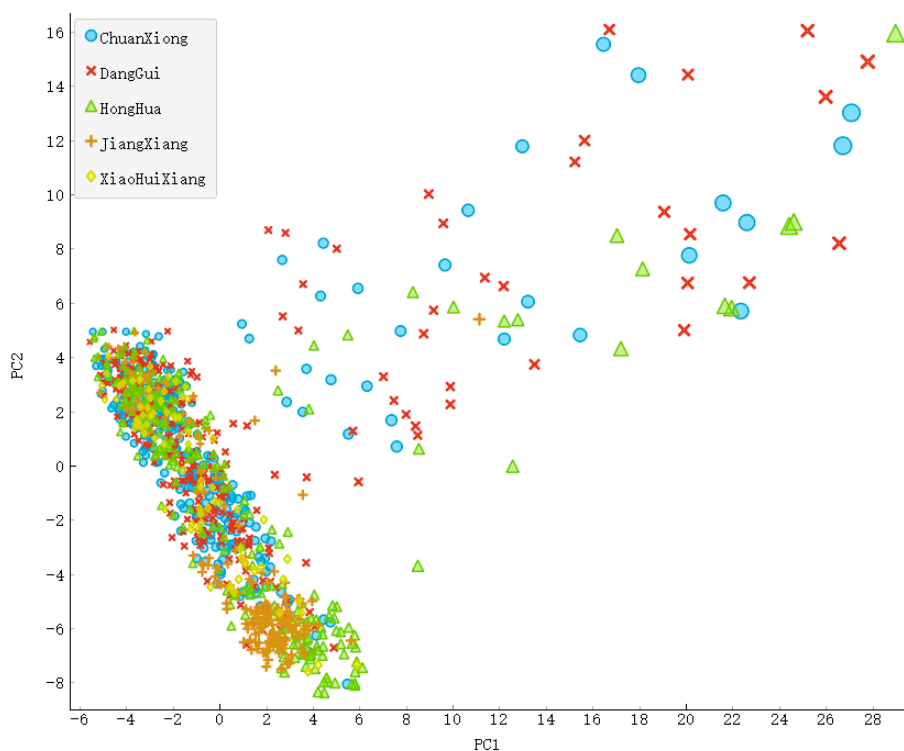
Figure 8. Five pungent TCMs' compounds PCA with Fingerprint of 166 bits.

4.2. The Gene Analysis of Liver and Heart Organ in Cardiovascular System

The targets of pungent flavor compounds associated with CVDs and liver diseases were obtained from literature mining and several disease-gene databases: DrugBank (http://www.drugbank.ca/) [162,163], STITCH (http://stitch.embl.de/) [164], ChEMBL (https://www.ebi.ac.uk/chembl/) [165], BindingDB (http://www.bindingdb.org/bind/index.jsp) [166,167]. Therapeutic Target Database (http://bidd.nus.edu.sg/group/ttd/) [173,174], and Comparative Toxicogenomics Database (CTD, http://ctdbase.org/) [175].

4.2.1. Identify the Pungent Flavored Compounds

The process of discovering the material basis of the pungent flavored TCMs can be clearly seen from Figure 1. The pungency is attributable to chemicals that activate a specific transient receptor potential (TRP) cation channel family. Moreover, the ligands of TRPs are most spices and flavor molecules. So, the spices flavor molecules were considered as the materials base of pungent flavor. The pungent flavored compounds of pungent TCMs are from Food Safety National Standard for use of food additives (GB2760-2014) [117] and flavorDB. The GB2760-2014 is the National Standard of Spice. FlavorDB [119] (http://cosylab.iiitd.edu.in/flavordb) comprises of 25,595 flavor molecules

representing an array of tastes and odors. Among these, 2254 molecules are associated with 936 natural ingredients belonging to 34 categories. Molecules from the chemical basis of flavor expressed primarily via gustatory and olfactory mechanisms [119]. The simple perception of pungent TCMs arises from the interaction of flavor molecules with the biological machinery by ancient medical practitioners' human sensory system. Flavors derived from TCMs have shaped the pungent flavor throughout ancient long-term clinical practice in China.

4.2.2. Identify Organ Target Location with Gene Organizer

The herb entering one meridian, or several meridians means the corresponding efficacy of such herb has obvious action towards this or these organs or meridian but no obvious effect to other parts. Due to the limitation of repertoire of expression datasets, there is a strong bias towards certain organs and tissues (e.g., brain, blood, and skin), and many other body parts are rare or completely absent. TCM theory has always focused on the interaction of TCMs with human body on a holistic view. Gene ORGANizer [134] was a comprehensive and fully curated Database, consisting of >150,000 gene-body part associations, and covering over 7000 human genes. So, Gene ORGANizer provides the strong evidence for elucidating the connotation of meridian tropism at the target level. The 5 pungent TCMs were all attributable to liver tropism. Moreover, among these pungent TCMs, *Carthami Flus* (Chinese name HongHua) and *Angelicae Sinensis Radix* (Chinese name DangGui), *Chuanxiong Rhizome* (Chinese name ChuanXiong) also belong to the heart or pericardium meridian tropism. The targets of pungent TCMs' pungent flavored compounds were mapped into the organ location map at the cardiovascular system level by Gene ORGANizer. We analyzed the correlation of genes associated with liver organ and heart organ based on phenotype.

4.3. Network Construction

To further elucidate multi-scale action mechanisms of pungent TCMs in the prevention and treatment of CVDs and liver diseases, we constructed two networks: Pungent Compound-Target network (C-T network) and Target-Pathway network (T-P network). In the network, the nodes represent compounds/targets/pathways, and edges represent they are linked with each other. The canonical pathways were extracted from the KEGG database (http://www.genome.jp/kegg/) [137,176]. The enriched KEGG pathways of targets with a false discovery rate of less than 0.005 by Fisher's Exact test in the DAVID database (https://david.ncifcrf.gov/) [177] were analyzed. In these networks, degree (DD) is used to characterize the connectedness of a node. The degree of a node is the number of edges associated with it. The networks were generated and analyzed by using Cytoscape 3.2.1 [178]. The topological properties of these networks were analyzed using the Network Analysis plugin CentiScaPe 1.2 of Cytoscape [179]. The degree of a node was defined as the number of edges connected to it, implying the importance of the node in a network.

5. Conclusions

In this study, we first proposed a novel strategy integrating target organ location, five flavor theory, and systems pharmacology approach to explore the molecular mechanism of pungent flavored compounds from pungent BASR TCMs in the synchronic treatment for cardiovascular diseases and liver diseases by acting on the heart and liver organ. Our main findings are as follows:

(1) The spice compounds were considered as the material basis of pungent flavor and their holistic efficacy at the special organ level.

(2) We systematically analyzed the relationship between pungent flavored compounds in pungent TCMs and their targets' organ location map.

(3) A novel system is constructed to investigate the closeness between targets of liver and heart in the cardiovascular system. The shared targets of liver and heart were identified, and the association was evaluated.

In summary, this study provided a systematic analysis of relationship between pungent compounds from pungent TCMs and the holistic efficacy of their targets in treating CVDs and liver diseases. We found potential active compounds to treat CVDs and liver diseases by the system pharmacology approach and understand the molecular mechanisms of how these 5 pungent TCMs treat CVDs and liver diseases by acting on heart organ and liver organ. Despite these potentially interesting findings above, further interpretation, such as the functional pungent flavor in TCMs and the herb dose-effect relationship, is necessary to be considered based on experimental data analysis. Moreover, further experimental testing of these pungent flavored compound-target binding actions and molecular mechanism of pungent flavored compounds from pungent TCMs in vivo will be required to support further assessments of potential clinical application.

Author Contributions: Z.C. formulated the idea of the paper and Y.Q. supervised the research. Y.Z. and Y.Q. performed the research. Z.C. draw the Figures 1–8. Z.C and Y.C. collected data. Z.C. wrote the paper. Y.Z., Y.C. and Y.Z. revised the paper. All authors reviewed the manuscript.

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

Abbreviations

BASR	blood-activating and stasis-resolving
cGMP-PKG	cyclic guanosine monophosphate-dependent protein kinase
CNS	central nervous system
CVDs	cardiovascular diseases
CYP1A1	cytochrome P450 1A1
JUN	proto-oncogene c-JUN
KEGG	Kyoto Encyclopedia of Genes and Genomes
LDL	low-density lipoprotein
MACCS	molecular Access System
MDL	Molecular Design Limited
NAFLD	non-alcoholic fatty liver disease
NFE2L2	nuclear factor erythroid 2-related factor 2
NFKB1	nuclear factor NF-kappa-B p105 subunit
PCA	Principal Component Analysis
PPARD	peroxisome proliferator-activated receptor delta,
PTGS2	prostaglandin G/H synthase 2
TCM	traditional Chinese medicine
TCM-HPs	traditional Chinese medicine herbal properties
TNF	tumor necrosis factor
TPAs	target-pathway association interactions
TRP	transient receptor potential
TRPA1	transient receptor potential ankyrin 1
TRPM7	potential cation channel, subfamily M, member 7
TRPM8	potential cation channel, subfamily M, member 8
TRPV1	transient receptor potential cation channel subfamily V member 1
TRPV3	transient receptor potential cation channel subfamily V member 3
VEGF	vascular endothelial growth factor

References

1. Kahleova, H.; Levin, S.; Barnard, N.D. Vegetarian dietary patterns and cardiovascular disease. *Prog. Cardiovasc. Dis.* **2018**, *61*, 54–61. [CrossRef] [PubMed]

2. North, B.J.; Sinclair, D.A. The intersection between aging and cardiovascular disease. *Circ. Res.* **2012**, *110*, 1097–1108. [CrossRef] [PubMed]

3. Lakatta, E.G.; Levy, D. Arterial and cardiac aging: Major shareholders in cardiovascular disease enterprises: Part I: Aging arteries: A "set up" for vascular disease. *Circulation* **2003**, *107*, 139–146. [CrossRef] [PubMed]

4. Humphries, K.H.; Izadnegahdar, M.; Sedlak, T.; Saw, J.; Johnston, N.; Schenck-Gustafsson, K.; Wei, J. Sex differences in cardiovascular disease-Impact on care and outcomes. *Front. Neuroendocrinol.* **2017**, *46*, 46–70. [CrossRef] [PubMed]

5. Xue, M.; Chen, K.; Yin, H. Relationship between platelet activation related factors and polymorphism of related genes in patients with coronary heart disease of blood-stasis syndrome. *Chin. J. Integr. Med.* **2008**, *14*, 267–273. [CrossRef] [PubMed]

6. Chiu, C.C.; Lan, C.Y.; Chang, Y.H. Objective assessment of blood stasis using computerized inspection of sublingual veins. *Comput. Methods Progr. Biomed.* **2002**, *69*, 1–12. [CrossRef]

7. Keji, C. *Cardiovascular Disease and Activating Blood Circulation to Remove Stasis*; Beijing Science & Technology Press: Beijing, China, 2009.

8. Lee, I.M.; Shiroma, E.J.; Lobelo, F.; Puska, P.; Blair, S.N.; Katzmarzyk, P.T. Lancet Physical Activity Series Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: An analysis of burden of disease and life expectancy. *Lancet* **2012**, *380*, 219–229. [CrossRef]

9. Gao, S.; Liu, Z.; Li, H.; Little, P.J.; Liu, P.; Xu, S. Cardiovascular actions and therapeutic potential of tanshinone IIA. *Atherosclerosis* **2012**, *220*, 3–10. [CrossRef]

10. Liu, X.H.; Li, L.Q.; Lu, W.H.; Lai, C.L. Effect of safflow yellow treatment on ET, MMP-9, hs-CRP and platelet aggregation rate of patients with coronary heart disease. *Chin. J. Integr. Med. Cardio-/Cerebrovasc. Dis.* **2011**, *9*, 1036–1037.

11. Tingmo, Z. *Chinese Materia Medica*; High Education Press: Beijing, China, 2008.

12. Tu, Y.; Xue, Y.; Guo, D.; Sun, L.; Guo, M. Carthami flos: A review of its ethnopharmacology, pharmacology and clinical applications. *Revista Brasileira de Farmacognosia* **2015**, *25*, 553–566. [CrossRef]

13. Ng, C.F.; Koon, C.M.; Cheung, D.W.S.; Lam, M.Y.; Leung, P.C.; Lau, C.B.S.; Fung, K.P. The anti-hypertensive effect of Danshen (Salvia miltiorrhiza) and Gegen (Pueraria lobata) formula in rats and its underlying mechanisms of vasorelaxation. *J. Ethnopharmacol.* **2011**, *137*, 1366–1372. [CrossRef] [PubMed]

14. Xie, W.; Zhao, Y.; Du, L. Emerging approaches of traditional Chinese medicine formulas for the treatment of hyperlipidemia. *J. Ethnopharmacol.* **2012**, *140*, 345–367. [CrossRef] [PubMed]

15. Chen, Z.; Zhang, C.; Gao, F.; Fu, Q.; Fu, C.; He, Y.; Zhang, J. A systematic review on the rhizome of Ligusticum chuanxiong Hort. (Chuanxiong). *Food Chem. Toxicol.* **2018**, *119*, 309–325. [CrossRef] [PubMed]

16. Mao, H.P.; Wang, X.Y.; Chang, Y.X.; Chen, L.; Niu, Z.C.; Ai, J.Q.; Gao, X.M. Danhong injection attenuates isoproterenol-induced cardiac hypertrophy by regulating p38 and NF-κb pathway. *J. Ethnopharmacol.* **2016**, *186*, 20–29. [CrossRef] [PubMed]

17. Crunkhorn, S. Cardiovascular disease: Spice might protect the heart. *Nat. Rev. Drug Discov.* **2008**, *7*, 389. [CrossRef]

18. Cao, C.M.; Xia, Q.; Zhang, X.; Xu, W.H.; Jiang, H.D.; Chen, J. Salvia miltiorrhiza attenuates the changes in contraction and intracellular calcium induced by anoxia and reoxygenation in rat cardiomyocytes. *Life Sci.* **2003**, *72*, 2451–2463. [CrossRef]

19. Yin, Y.; Guan, Y.; Duan, J.; Wei, G.; Zhu, Y.; Quan, W.; Wen, A. Cardioprotective effect of Danshensu against myocardial ischemia/reperfusion injury and inhibits apoptosis of H9c2 cardiomyocytes via Akt and ERK1/2 phosphorylation. *Eur. J. Pharmacol.* **2013**, *699*, 219–226. [CrossRef]

20. Ma, X.J.; Yin, S.J.; Jin, J.C.; Wu, C.F.; Huang, Y.; Shi, D.Z.; Yin, H.J. Synergistic protection of Danhong Injection and ischemic postconditioning on myocardial reperfusion injury in minipigs. *Chin. J. Integr. Med.* **2010**, *16*, 531–536. [CrossRef]

21. Jia, Y.; Huang, F.; Zhang, S.; Leung, S.W. Is danshen (Salvia miltiorrhiza) dripping pill more effective than isosorbide dinitrate in treating angina pectoris? A systematic review of randomized controlled trials. *Int. J. Cardiol.* **2012**, *157*, 330–340. [CrossRef]

22. Kang, D.G.; Yun, Y.G.; Ryoo, J.H.; Lee, H.S. Anti-hypertensive effect of water extract of danshen on renovascular hypertension through inhibition of the renin angiotensin system. *Am. J. Chin. Med.* **2002**, *30*, 87–93. [CrossRef]

23. Fan, H.; Li, M.; Yu, L.; Jin, W.; Yang, J.; Zhang, Y.; Wan, H. Effects of Danhong injection on platelet aggregation in hyperlipidemia rats. *J. Ethnopharmacol.* **2018**, *212*, 67–73. [CrossRef]

24. Marcellin, P.; Kutala, B.K. Liver diseases: A major, neglected global public health problem requiring urgent actions and large-scale screening. *Liver Int.* **2018**, *38*, 2–6. [CrossRef] [PubMed]

25. Mokdad, A.A.; Lopez, A.D.; Shahraz, S.; Lozano, R.; Mokdad, A.H.; Stanaway, J.; Naghavi, M. Liver cirrhosis mortality in 187 countries between 1980 and 2010: A systematic analysis. *BMC Med.* **2014**, *12*, 145. [CrossRef]

26. Murray, C.J.; Vos, T.; Lozano, R.; Naghavi, M.; Flaxman, A.D.; Michaud, C.; Aboyans, V. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **2012**, *380*, 2197–2223. [CrossRef]

27. Yang, S.S. Alcoholic Liver Disease in the Asian–Pacific Region with High Prevalence of Chronic Viral Hepatitis. *J. Med. Ultrasound* **2016**, *24*, 93–100. [CrossRef]

28. Estes, C.; Anstee, Q.M.; Arias-Loste, M.T.; Bantel, H.; Bellentani, S.; Caballeria, J.; Geier, A. Modeling NAFLD Disease Burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J. Hepatol.* **2018**, *69*, 896–904. [CrossRef] [PubMed]

29. Vernon, G.; Baranova, A.; Younossi, Z.M. Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment. Pharmacol. Ther.* **2011**, *34*, 274–285. [CrossRef] [PubMed]

30. Fan, J.G.; Kim, S.U.; Wong, V.W.S. New trends on obesity and NAFLD in Asia. *J. Hepatol.* **2017**, *67*, 862–873. [CrossRef] [PubMed]

31. World Health Organization (WHO). Obesity and Overweight. Available online: http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed on 18 January 2019).

32. Lebeaupin, C.; Vallée, D.; Hazari, Y.; Hetz, C.; Chevet, E.; Bailly-Maitre, B. Endoplasmic Reticulum stress signaling and the pathogenesis of Non-Alcoholic Fatty Liver Disease. *J. Hepatol.* **2018**, *69*, 927–947. [CrossRef]

33. Chalasani, N.; Younossi, Z.; Lavine, J.E.; Charlton, M.; Cusi, K.; Rinella, M.; Sanyal, A.J. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* **2017**, *67*, 328–357. [CrossRef]

34. Younossi, Z.; Henry, L. Contribution of alcoholic and nonalcoholic fatty liver disease to the burden of liver-related morbidity and mortality. *Gastroenterology* **2016**, *150*, 1778–1785. [CrossRef]

35. Younossi, Z.M.; Blissett, D.; Blissett, R.; Henry, L.; Stepanova, M.; Younossi, Y.; Beckerman, R. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology* **2016**, *64*, 1577–1586. [CrossRef]

36. European Association for the Study of the Liver; European Association for the Study of Diabetes (EASD). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *Obes. Facts* **2016**, *9*, 65–90. [CrossRef]

37. Angulo, P.; Kleiner, D.E.; Dam-Larsen, S.; Adams, L.A.; Bjornsson, E.S.; Charatcharoenwitthaya, P.; Haflidadottir, S. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* **2015**, *149*, 389–397. [CrossRef] [PubMed]

38. Bhala, N.; Angulo, P.; van der Poorten, D.; Lee, E.; Hui, J.M.; Saracco, G.; Day, C.P. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: An international collaborative study. *Hepatology* **2011**, *54*, 1208–1216. [CrossRef] [PubMed]

39. Ekstedt, M.; Hagström, H.; Nasr, P.; Fredrikson, M.; Stål, P.; Kechagias, S.; Hultcrantz, R. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* **2015**, *61*, 1547–1554. [CrossRef] [PubMed]

40. Hagström, H.; Nasr, P.; Ekstedt, M.; Hammar, U.; Stål, P.; Hultcrantz, R.; Kechagias, S. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. *J. Hepatol.* **2017**, *67*, 1265–1273. [CrossRef] [PubMed]

41. Cheung, F. Made in china. *Nature* **2011**, *480*, S82–S83. [CrossRef] [PubMed]

42. Qiu, J. China plans to modernize traditional medicine. *Nature* **2007**, *446*, 590–591. [CrossRef]

43. Qiu, J. Traditional medicine: A culture in the balance. *Nature* **2007**, *448*, 126–128. [CrossRef]

44. Science, A.A.F.T. The art and science of traditional medicine part 1: TCM today—A case for integration. *Science* **2014**, *346*, 1569.

45. Xue, R.; Fang, Z.; Zhang, M.; Yi, Z.; Wen, C.; Shi, T. TCMID: Traditional Chinese medicine integrative database for herb molecular mechanism analysis. *Nucleic Acids Res.* **2012**, *41*, D1089–D1095. [CrossRef] [PubMed]

46. Huang, L.; Xie, D.; Yu, Y.; Liu, H.; Shi, Y.; Shi, T.; Wen, C. TCMID 2.0: A comprehensive resource for TCM. *Nucleic Acids Res.* **2018**, *46*, D1117–D1120. [CrossRef] [PubMed]

47. *Spices—A Survey of the World Market*; Geneva, Switzerland, 1982; Volume 1, pp. 68–712.

48. Billing, J.A.P.W. Antimicrobial functions of spices: Why some like it hot. *Q. Rev. Biol.* **1998**, *73*, 3–49. [CrossRef] [PubMed]

49. Pavithra, G. Effect of Spices on Bacteria—A Short Review. *J. Pharm. Sci. Res.* **2014**, *6*, 268–270.

50. Arora, D.S.; Kaur, J. Antimicrobial activity of spices. *Int. J. Antimicrob. Agents* **1999**, *12*, 257–262. [CrossRef]

51. Srinivasan, K. Role of spices beyond food flavoring: Nutraceuticals with multiple health effects. *Food Rev. Int.* **2005**, *21*, 167–188. [CrossRef]

52. Tapsell, L.C.; Hemphill, I.; Cobiac, L.; Patch, C.S.; Sullivan, D.R.; Fenech, M.; Roodenrys, S.; Keogh, J.B.; Clifton, P.M.; Williams, P.G.; et al. Health benefits of herbs and spices: The past, the present, the future. *Med. J. Aust.* **2006**, *185*, S4–24.

53. Gore, J.M.; Dalen, J.E. Cardiovascular disease. *JAMA-J. Am. Med. Assoc.-US Ed.* **1994**, *271*, 1660–1661. [CrossRef]

54. Warshafsky, S.; Kamer, R.S.; Sivak, S.L. Effect of garlic on total serum cholesterol: A meta-analysis. *Ann. Intern. Med.* **1993**, *119*, 599–605. [CrossRef]

55. Sofos, J.N.; Beuchat, L.R.; Davidson, P.M.; Johnson, E.A. Naturally occurring antimicrobials in food. *Regul. Toxicol. Pharmacol.* **1998**, *28*, 71–72. [CrossRef] [PubMed]

56. Beuchat, L.R. Antimicrobial properties of spices and their essential oils. *Nat. Antimicrob. Syst. Food Preserv.* **1994**, *12*, 257–262.

57. Liu, Q.; Meng, X.; Li, Y.; Zhao, C.; Tang, G.; Li, H. Antibacterial and Antifungal Activities of Spices. *Int. J. Mol. Sci.* **2017**, *18*, 1283. [CrossRef] [PubMed]

58. Tajkarimi, M.M.; Ibrahim, S.A.; Cliver, D.O. Antimicrobial herb and spice compounds in food. *Food Control* **2010**, *21*, 1199–1218. [CrossRef]

59. Clapham, D.E. TRP channels as cellular sensors. *Nature* **2003**, *426*, 517. [CrossRef] [PubMed]

60. Kichko, T.I.; Neuhuber, W.; Kobal, G.; Reeh, P.W. The roles of TRPV1, TRPA1 and TRPM8 channels in chemical and thermal sensitivity of the mouse oral mucosa. *Eur. J. Neurosci.* **2018**, *47*, 201–210. [CrossRef]

61. Everaerts, W.; Gees, M.; Alpizar, Y.A.; Farre, R.; Leten, C.; Apetrei, A.; Nilius, B. The capsaicin receptor TRPV1 is a crucial mediator of the noxious effects of mustard oil. *Curr. Biol.* **2011**, *21*, 316–321. [CrossRef]

62. Moparthi, L.; Kichko, T.I.; Eberhardt, M.; Högestätt, E.D.; Kjellbom, P.; Johanson, U.; Zygmunt, P.M. Human TRPA1 is a heat sensor displaying intrinsic U-shaped thermosensitivity. *Sci. Rep.-UK* **2016**, *6*, 28763. [CrossRef]

63. Peier, A.M.; Moqrich, A.; Hergarden, A.C.; Reeve, A.J.; Andersson, D.A.; Story, G.M.; Patapoutian, A. A TRP channel that senses cold stimuli and menthol. *Cell* **2002**, *108*, 705–715. [CrossRef]

64. Bandell, M.; Story, G.M.; Hwang, S.W.; Viswanath, V.; Eid, S.R.; Petrus, M.J.; Patapoutian, A. Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin. *Neuron* **2004**, *41*, 849–857. [CrossRef]

65. Bautista, D.M.; Movahed, P.; Hinman, A.; Axelsson, H.E.; Sterner, O.; Högestätt, E.D.; Zygmunt, P.M. Pungent products from garlic activate the sensory ion channel TRPA1. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 12248–12252. [CrossRef] [PubMed]

66. Jordt, S.E.; Bautista, D.M.; Chuang, H.H.; McKemy, D.D.; Zygmunt, P.M.; Högestätt, E.D.; Julius, D. Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. *Nature* **2004**, *427*, 260. [CrossRef] [PubMed]

67. Macpherson, L.J.; Geierstanger, B.H.; Viswanath, V.; Bandell, M.; Eid, S.R.; Hwang, S.; Patapoutian, A. The pungency of garlic: Activation of TRPA1 and TRPV1 in response to allicin. *Curr. Biol.* **2005**, *15*, 929–934. [CrossRef] [PubMed]

68. Salazar, H.; Llorente, I.; Jara-Oseguera, A.; García-Villegas, R.; Munari, M.; Gordon, S.E.; Islas, L.D.; Rosenbaum, T. A single N-terminal cysteine in TRPV1 determines activation by pungent compounds from onion and garlic. *Nat. Neurosci.* **2008**, *11*, 255–261. [CrossRef]

69. Dhaka, A.; Viswanath, V.; Patapoutian, A. Trp ion channels and temperature sensation. *Annu. Rev. Neurosci.* **2006**, *29*, 135–161. [CrossRef]

70. Chung, G.; Im, S.T.; Kim, Y.H.; Jung, S.J.; Rhyu, M.R.; Oh, S.B. Activation of transient receptor potential ankyrin 1 by eugenol. *Neuroscience* **2014**, *261*, 153–160. [CrossRef] [PubMed]

71. Brierley, S.M.; Kelber, O. Use of natural products in gastrointestinal therapies. *Curr. Opin. Pharmacol.* **2011**, *11*, 604–611. [CrossRef] [PubMed]

72. Earley, S.; Gonzales, A.L.; Garcia, Z.I. A dietary agonist of TRPV3 elicits endothelium-dependent vasodilation. *Mol. Pharmacol.* **2010**, *77*, 612–620. [CrossRef]

73. Ueda, T.; Yamada, T.; Ugawa, S.; Ishida, Y.; Shimada, S. TRPV3, a thermosensitive channel is expressed in mouse distal colon epithelium. *Biochem. Biophys. Res. Commun.* **2009**, *383*, 130–134. [CrossRef]

74. Vennekens, R.; Vriens, J.; Nilius, B. Herbal compounds and toxins modulating TRP channels. *Curr. Neuropharmacol.* **2008**, *6*, 79–96. [CrossRef]

75. Baraldi, P.G.; Preti, D.; Materazzi, S.; Geppetti, P. Transient receptor potential ankyrin 1 (TRPA1) channel as emerging target for novel analgesics and anti-inflammatory agents. *J. Med. Chem.* **2010**, *53*, 5085–5107. [CrossRef] [PubMed]

76. Hasan, R.; Leeson-Payne, A.T.S.; Jaggar, J.H.; Zhang, X. Calmodulin is responsible for Ca 2+-dependent regulation of TRPA1 Channels. *Sci. Rep.* **2017**, *7*, 45098. [CrossRef] [PubMed]

77. Bae, C.Y.J.; Sun, H. Current understanding of TRPM7 pharmacology and drug development for stroke. *Acta Pharmacol. Sin.* **2013**, *34*, 10. [CrossRef] [PubMed]

78. Kurzawski, M.; Dziedziejko, V.; Urasińska, E.; Post, M.; Wójcicki, M.; Miętkiewski, J.; Droździk, M. Nuclear factor erythroid 2-like 2 (Nrf2) expression in end-stage liver disease. *Environ. Toxicol. Phar.* **2012**, *34*, 87–95. [CrossRef] [PubMed]

79. Olagnier, D.; Brandtoft, A.M.; Gunderstofte, C.; Villadsen, N.L.; Krapp, C.; Thielke, A.L.; Thyrsted, J. Nrf2 negatively regulates STING indicating a link between antiviral sensing and metabolic reprogramming. *Nat. Commun.* **2018**, *9*, 3506. [CrossRef] [PubMed]

80. Lamlé, J.; Marhenke, S.; Borlak, J.; Von Wasielewski, R.; Eriksson, C.P.; Geffers, R.; Vogel, A. Nuclear Factor-Eythroid 2–Related Factor 2 Prevents Alcohol-Induced Fulminant Liver Injury. *Gastroenterology* **2008**, *134*, 1159–1168. [CrossRef]

81. Harrison, D.; Griendling, K.K.; Landmesser, U.; Hornig, B.; Drexler, H. Role of oxidative stress in atherosclerosis. *Am. J. Cardiol.* **2003**, *91*, 7–11. [CrossRef]

82. Collins, A.R.; Gupte, A.A.; Ji, R.; Ramirez, M.R.; Minze, L.J.; Liu, J.Z.; Lyon, C.J. Myeloid deletion of nuclear factor erythroid 2−related factor 2 increases atherosclerosis and liver injury. *Arterioscler. Thromb. Vasc. Biol.* **2012**, *32*, 2839–2846. [CrossRef]

83. Ruotsalainen, A.K.; Inkala, M.; Partanen, M.E.; Lappalainen, J.P.; Kansanen, E.; Mäkinen, P.I.; Hörkkö, S. The absence of macrophage Nrf2 promotes early atherogenesis. *Cardiovasc. Res.* **2013**, *98*, 107–115. [CrossRef]

84. Harrison, D.G.; Gongora, M.C. Oxidative stress and hypertension. *Med. Clin.* **2009**, *93*, 621–635. [CrossRef]

85. Cifuentes, M.E.; Pagano, P.J. Targeting reactive oxygen species in hypertension. *Curr. Opin. Nephrol. Hypertens.* **2006**, *15*, 179–186. [CrossRef] [PubMed]

86. Delles, C.; Miller, W.H.; Dominiczak, A.F. Targeting reactive oxygen species in hypertension. *Antioxid. Redox Signal.* **2008**, *10*, 1061–1078. [CrossRef] [PubMed]

87. Mehta, P.K.; Griendling, K.K. Angiotensin II cell signaling: Physiological and pathological effects in the cardiovascular system. *Am. J. Physiol.-Cell Physiol.* **2007**, *292*, C82–C97. [CrossRef] [PubMed]

88. Li, J.; Ichikawa, T.; Villacorta, L.; Janicki, J.S.; Brower, G.L.; Yamamoto, M.; Cui, T. Nrf2 protects against maladaptive cardiac responses to hemodynamic stress. *Arterioscler. Thromb. Vasc. Biol.* **2009**, *29*, 1843–1850. [CrossRef] [PubMed]

89. Brewer, A.C.; Murray, T.V.; Arno, M.; Zhang, M.; Anilkumar, N.P.; Mann, G.E.; Shah, A.M. Nox4 regulates Nrf2 and glutathione redox in cardiomyocytes in vivo. *Free Radic. Biol. Med.* **2011**, *51*, 205–215. [CrossRef] [PubMed]

90. Kuroda, J.; Ago, T.; Matsushima, S.; Zhai, P.; Schneider, M.D.; Sadoshima, J. NADPH oxidase 4 (Nox4) is a major source of oxidative stress in the failing heart. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 15565–15570. [CrossRef] [PubMed]

91. Ichikawa, T.; Li, J.; Meyer, C.J.; Janicki, J.S.; Hannink, M.; Cui, T. Dihydro-CDDO-trifluoroethyl amide (dh404), a novel Nrf2 activator, suppresses oxidative stress in cardiomyocytes. *PLoS ONE* **2009**, *4*, e8391. [CrossRef]

92. Bailey-Downs, L.C.; Mitschelen, M.; Sosnowska, D.; Toth, P.; Pinto, J.T.; Ballabh, P.; Bass, C. Liver-specific knockdown of IGF-1 decreases vascular oxidative stress resistance by impairing the Nrf2-dependent antioxidant response: A novel model of vascular aging. *J. Gerontol. Ser. A Biomed. Sci. Med. Sci.* **2011**, *67*, 313–329. [CrossRef]

93. Dai, G.; Vaughn, S.; Zhang, Y.; Wang, E.T.; Garcia-Cardena, G.; Gimbrone, M.A. Biomechanical forces in atherosclerosis-resistant vascular regions regulate endothelial redox balance via phosphoinositol 3-kinase/Akt-dependent activation of Nrf2. *Circ. Res.* **2007**, *101*, 723–733. [CrossRef]

94. Hosoya, T.; Maruyama, A.; Kang, M.I.; Kawatani, Y.; Shibata, T.; Uchida, K.; Yamamoto, M. Differential responses of the Nrf2-Keap1 system to laminar and oscillatory shear stresses in endothelial cells. *J. Biol. Chem.* **2005**, *280*, 27244–27250. [CrossRef]

95. Jyrkkänen, H.K.; Kansanen, E.; Inkala, M.; Kivelä, A.M.; Hurttila, H.; Heinonen, S.E.; Oskolkova, O. Nrf2 regulates antioxidant gene expression evoked by oxidized phospholipids in endothelial cells and murine arteries in vivo. *Circ. Res.* **2008**, *103*, e1–e9. [CrossRef] [PubMed]

96. Ungvari, Z.; Bagi, Z.; Feher, A.; Recchia, F.A.; Sonntag, W.E.; Pearson, K.; Csiszar, A. Resveratrol confers endothelial protection via activation of the antioxidant transcription factor Nrf2. *Am. J. Physiol.-Heart Circ.* **2010**, *299*, H18–H24. [CrossRef] [PubMed]

97. Nigro, P.; Abe, J.I.; Berk, B.C. Flow shear stress and atherosclerosis: A matter of site specificity. *Antioxid. Redox Signal.* **2011**, *15*, 1405–1414. [CrossRef] [PubMed]

98. Choi, J.H.; Jin, S.W.; Kim, H.G.; Khanal, T.; Hwang, Y.P.; Lee, K.J.; Jeong, H.G. Platycodi Radix attenuates dimethylnitrosamine-induced liver fibrosis in rats by inducing Nrf2-mediated antioxidant enzymes. *Food Chem. Toxicol.* **2013**, *56*, 231–239. [CrossRef] [PubMed]

99. Xu, W.; Hellerbrand, C.; Köhler, U.A.; Bugnon, P.; Kan, Y.W.; Werner, S.; Beyer, T.A. The Nrf2 transcription factor protects from toxin-induced liver injury and fibrosis. *Lab Investig.* **2008**, *88*, 1068. [CrossRef] [PubMed]

100. Xing, Y.; Niu, T.; Wang, W.; Li, J.; Li, S.; Janicki, J.S.; Zhao, Y. Triterpenoid dihydro-CDDO-trifluoroethyl amide protects against maladaptive cardiac remodeling and dysfunction in mice: A critical role of Nrf2. *PLoS ONE* **2012**, *7*, e44899. [CrossRef] [PubMed]

101. Yu, Z.; Shao, W.; Chiang, Y.; Foltz, W.; Zhang, Z.; Ling, W.; Jin, T. Oltipraz upregulates the nuclear respiratory factor 2 alpha subunit (NRF2) antioxidant system and prevents insulin resistance and obesity induced by a high-fat diet in C57BL/6J mice. *Diabetologia* **2011**, *54*, 922–934. [CrossRef]

102. Migeon, B.R.; Brown, T.R.; Axelman, J.; Migeon, C.J. Studies of the locus for androgen receptor: Localization on the human X chromosome and evidence for homology with the Tfm locus in the mouse. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 6339–6343. [CrossRef]

103. Gao, W.; Bohl, C.E.; Dalton, J.T. Chemistry and structural biology of androgen receptor. *Chem. Rev.* **2005**, *105*, 3352–3370. [CrossRef]

104. Mangelsdorf, D.J.; Thummel, C.; Beato, M.; Herrlich, P.; Schütz, G.; Umesono, K.; Evans, R.M. The nuclear receptor superfamily: The second decade. *Cell* **1995**, *83*, 835–839. [CrossRef]

105. Eisenfeld, A.J.; Aten, R.F. Estrogen receptors and androgen receptors in the mammalian liver. *J. Steroid Biochem.* **1987**, *27*, 1109–1118. [CrossRef]

106. Winborn, W.B.; Sheridan, P.J.; McGill, H.C. Sex steroid receptors in the stomach, liver, pancreas, and gastrointestinal tract of the baboon. *Gastroenterology* **1987**, *92*, 23–32. [CrossRef]

107. Keller, E.T.; Ershler, W.B.; Chang, C. The androgen receptor: A mediator of diverse responses. *Front. Biosci.* **1996**, *1*, d59-71. [PubMed]

108. Zhu, D.; Hadoke, P.W.; Wu, J.; Vesey, A.T.; Lerman, D.A.; Dweck, M.R.; MacRae, V.E. Ablation of the androgen receptor from vascular smooth muscle cells demonstrates a role for testosterone in vascular calcification. *Sci. Rep.-UK* **2016**, *6*, 24807. [CrossRef] [PubMed]

109. Crabbe, P.; Bogaert, V.; De Bacquer, D.; Goemaere, S.T.E.F.; Zmierczak, H.; Kaufman, J.M. Part of the interindividual variation in serum testosterone levels in healthy men reflects differences in androgen sensitivity and feedback set point: Contribution of the androgen receptor polyglutamine tract polymorphism. *J. Clin. Endocrinol. Metab.* **2007**, *92*, 3604–3610. [CrossRef] [PubMed]

110. Page, S.T.; Kupelian, V.; Bremner, W.J.; McKinlay, J.B. The androgen receptor gene CAG repeat polymorphism does not predict increased risk of heart disease: Longitudinal results from the Massachusetts Male Ageing Study. *Clin. Endocrinol.* **2006**, *65*, 333–339. [CrossRef] [PubMed]

111. Guengerich, F.P.; Shimada, T. Oxidation of toxic and carcinogenic chemicals by human cytochrome P-450 enzymes. *Chem. Res. Toxicol.* **1991**, *4*, 391–407. [CrossRef] [PubMed]

112. Wrighton, S.A.; Stevens, J.C. The human hepatic cytochromes P450 involved in drug metabolism. *Crit. Rev. Toxicol.* **1992**, *22*, 1–21. [CrossRef]

113. Preissner, S.C.; Hoffmann, M.F.; Preissner, R.; Dunkel, M.; Gewiess, A.; Preissner, S. Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. *PLoS ONE* **2013**, *8*, e82562. [CrossRef]

114. Culhane, A.C.; Schwarzl, T.; Sultana, R.; Picard, K.C.; Picard, S.C.; Lu, T.H.; Quackenbush, J. GeneSigDB—A curated database of gene expression signatures. *Nucleic Acids Res.* **2009**, *38*, D716–D725. [CrossRef]

115. Thum, T.; Borlak, J. Gene expression in distinct regions of the heart. *Lancet* **2000**, *355*, 979–983. [CrossRef]

116. Gebremichael, A.; Chang, A.M.; Buckpitt, A.R.; Plopper, C.G.; Pinkerton, K.E. Postnatal development of cytochrome P4501A1 and 2B1 in rat lung and liver: Effect of aged and diluted sidestream cigarette smoke. *Toxicol. Appl. Pharm.* **1995**, *135*, 246–253. [CrossRef] [PubMed]

117. Uno, S.; Nebert, D.W.; Makishima, M. Cytochrome P450 1A1 (CYP1A1) protects against nonalcoholic fatty liver disease caused by Western diet containing benzo [a] pyrene in mice. *Food Chem. Toxicol.* **2018**, *113*, 73–82. [CrossRef] [PubMed]

118. Ozeki, J.; Uno, S.; Ogura, M.; Choi, M.; Maeda, T.; Sakurai, K.; Makishima, M. Aryl hydrocarbon receptor ligand 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin enhances liver damage in bile duct-ligated mice. *Toxicology* **2011**, *280*, 10–17. [CrossRef] [PubMed]

119. Yamazaki, Y.; Hashida, H.; Arita, A.; Hamaguchi, K.; Shimura, F. High dose of commercial products of kava (Piper methysticum) markedly enhanced hepatic cytochrome P450 1A1 mRNA expression with liver enlargement in rats. *Food Chem. Toxicol.* **2008**, *46*, 3732–3738. [CrossRef] [PubMed]

120. Harrigan, J.A.; McGarrigle, B.P.; Sutter, T.R.; Olson, J.R. Tissue specific induction of cytochrome P450 (CYP) 1A1 and 1B1 in rat liver and lung following in vitro (tissue slice) and in vivo exposure to benzo (a) pyrene. *Toxicol. In Vitro* **2006**, *20*, 426–438. [CrossRef] [PubMed]

121. Wong, C.K.; Yeung, H.Y.; Woo, P.S.; Wong, M.H. Specific expression of cytochrome P4501A1 gene in gill, intestine and liver of tilapia exposed to coastal sediments. *Aquat. Toxicol.* **2001**, *54*, 69–80. [CrossRef]

122. Wong, C.K.C.; Yeung, H.Y.; Cheung, R.Y.H.; Yung, K.K.L.; Wong, M.H. Ecotoxicological assessment of persistent organic and heavy metal contamination in Hong Kong coastal sediment. *Arch. Environ. Contam. Toxicol.* **2000**, *38*, 486–493. [CrossRef]

123. White, R.D.; Shea, D.; Coloww, A.R.; Stegeman, J.J. Induction and post-transcriptional suppression of hepatic cytochrome P450 1A1 by 3, 3′, 4, 4′-tetrachlorobiphenyl. *Biochem. Pharmacol.* **1997**, *53*, 1029–1040. [CrossRef]

124. Almli, B.; Egaas, E.; Christiansen, A.; Eklo, O.M.; Lode, O.; Källqvist, T. Effects of three fungicides alone and in combination on glutathione S-transferase activity (GST) and cytochrome P-450 (CYP 1A1) in the liver and gill of brown trout (Salmo trutta). *Mar. Environ. Res.* **2002**, *54*, 237–240. [CrossRef]

125. Petkam, R.; Renaud, R.L.; Leatherland, J.F. The role of CYP 1A1 in the in vitro metabolism of pregnenolone by the liver of rainbow trout embryos. *Comp. Bioch. Physiol. Part C Toxicol. Pharmacol.* **2003**, *135*, 277–284. [CrossRef]

126. Stiborová, M.; Martínek, V.; Rýdlová, H.; Koblas, T.; Hodek, P. Expression of cytochrome P450 1A1 and its contribution to oxidation of a potential human carcinogen 1-phenylazo-2-naphthol (Sudan I) in human livers. *Cancer Lett.* **2005**, *220*, 145–154. [CrossRef] [PubMed]

127. Huang, P.; Ceccatelli, S.; Rannug, A. A study on diurnal mRNA expression of CYP1A1, AHR, ARNT, and PER2 in rat pituitary and liver. *Environ. Toxicol. Pharmacol.* **2002**, *11*, 119–126. [CrossRef]

128. Badawi, A.F.; Cavalieri, E.L.; Rogan, E.G. Role of human cytochrome P450 1A1, 1A2, 1B1, and 3A4 in the 2-, 4-, and 16 [alpha]-hydroxylation of 17 [beta]-estradiol. *Metabolism* **2001**, *50*, 1001–1003. [CrossRef]

129. Bindea, G.; Mlecnik, B.; Hackl, H.; Charoentong, P.; Tosolini, M.; Kirilovsky, A.; Galon, J. ClueGO: A Cytoscape plug-in to decipher functionally grouped gene ontology and pathway annotation networks. *Bioinformatics* **2009**, *25*, 1091–1093. [CrossRef]

130. Huang, D.W.; Sherman, B.T.; Lempicki, R.A. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat. Protoc.* **2008**, *4*, 44. [CrossRef]

131. Wu, C.; MacLeod, I.; Su, A.I. BioGPS and MyGene. info: Organizing online, gene-centric information. *Nucleic Acids Res.* **2012**, *41*, D561–D565. [CrossRef]

132. Wu, C.; Orozco, C.; Boyer, J.; Leglise, M.; Goodale, J.; Batalov, S.; Su, A.I.B.A. BioGPS: An extensible and customizable portal for querying and organizing gene annotation resources. *Genome Biol.* **2009**, *10*, R130. [CrossRef]

133. Park, J.; Lee, D.S.; Christakis, N.A.; Barabási, A.L. The impact of cellular networks on disease comorbidity. *Mol. Syst. Biol.* **2009**, *5*, 262. [CrossRef]

134. Gokhman, D.; Kelman, G.; Amartely, A.; Gershon, G.; Tsur, S.; Carmel, L. Gene ORGANizer: Linking genes to the organs they affect. *Nucleic Acids Res.* **2017**, *45*, W138–W145. [CrossRef]

135. Zhang, W.; Tao, Q.; Guo, Z.; Fu, Y.; Chen, X.; Shar, P.A.; Wu, Z.; Wang, Z. Systems Pharmacology Dissection of the Integrated Treatment for Cardiovascular and Gastrointestinal Disorders by Traditional Chinese Medicine. *Sci. Rep.-UK* **2016**, *6*, 32400. [CrossRef] [PubMed]

136. Gao, L.; Wang, X.; Niu, Y.; Duan, D.; Yang, X.; Hao, J.; Zhu, C.; Chen, D.; Wang, K.; Qin, X.; Wu, X. Molecular targets of Chinese herbs: A clinical study of hepatoma based on network pharmacology. *Sci. Rep.-UK* **2016**, *6*, 24944. [CrossRef] [PubMed]

137. Kanehisa, M.; Goto, S. KEGG: Kyoto encyclopedia of genes and genomes. *Nucleic Acids Res.* **2000**, *28*, 27–30. [CrossRef] [PubMed]

138. Marks, A.R. Ryanodine receptors/calcium release channels in heart failure and sudden cardiac death. *J. Mol. Cell Cardiol.* **2001**, *33*, 615–624. [CrossRef] [PubMed]

139. Bradshaw, R.A.; Dennis, E.A.E. *Handbook of Cell Signaling*; Academic Press: New York, NY, USA, 2009.

140. Birschmann, I.; Walter, U. Physiology and pathophysiology of vascular signaling controlled by guanosine 3′, 5′-cyclic monophosphate-dependent protein kinase. *Acta Biochim. Pol.* **2004**, *51*, 397–404. [PubMed]

141. Kong, Q.; Blanton, R.M. Protein kinase GI and heart failure: Shifting focus from vascular unloading to direct myocardial antiremodeling effects. *Circ. Heart Fail.* **2013**, *6*, 1268–1283. [CrossRef] [PubMed]

142. Taylor, R.N.; Roberts, J.M.; Cunningham, F.G.; Lindheimer, M.D.E. *Chesley's Hypertensive Disorders in Pregnancy*; Elsevier: Amsterdam, The Netherlands, 2014.

143. Meyer, J.; Lejmi, E.; Fontana, P.; Morel, P.; Gonelle-Gispert, C.; Bühler, L. A focus on the role of platelets in liver regeneration: Do platelet-endothelial cell interactions initiate the regenerative process? *J. Hepatol.* **2015**, *63*, 1263–1271. [CrossRef] [PubMed]

144. Fuentes, E.; Gibbins, J.M.; Holbrook, L.M.; Palomo, I. Nadph Oxidase 2 (Nox2): A Key Target of Oxidative Stress-Mediated Platelet Activation and Thrombosis. *Trends Cardiovasc. Med.* **2018**, *28*, 429–434. [CrossRef] [PubMed]

145. Faggio, C.; Sureda, A.; Morabito, S.; Sanches-Silva, A.; Mocan, A.; Nabavi, S.F.; Nabavi, S.M. Flavonoids and platelet aggregation: A brief review. *Eur. J. Pharmacol.* **2017**, *807*, 91–101. [CrossRef] [PubMed]

146. Bodin, S.; Tronchère, H.; Payrastre, B. Lipid rafts are critical membrane domains in blood platelet activation processes. *Biochim. Biophys. Acta (BBA)-Biomembr.* **2003**, *1610*, 247–257. [CrossRef]

147. Touyz, R.M.; Herrmann, S.; Herrmann, J. Vascular toxicities with VEGF inhibitor therapies-Focus on Hypertension and Arterial Thrombotic Events. *J. Am. Soc. Hypertens.* **2018**, *12*, 409–425. [CrossRef] [PubMed]

148. Xin, H.; Zhong, C.; Nudleman, E.; Ferrara, N. Evidence for pro-angiogenic functions of VEGF-Ax. *Cell* **2016**, *167*, 275–284. [CrossRef]

149. Roskoski, R., Jr. Vascular endothelial growth factor (VEGF) and VEGF receptor inhibitors in the treatment of renal cell carcinomas. *Pharmacol. Res.* **2017**, *120*, 116–132. [CrossRef]

150. Teschke, R.; Xuan, T.D. A Contributory Role of Shell Ginger (Alpinia zerumbet) for Human Longevity in Okinawa, Japan? *Nutrients* **2018**, *10*, 166. [CrossRef] [PubMed]

151. Ung, C.Y.; Li, H.; Kong, C.Y.; Wang, J.F.; Chen, Y.Z. Usefulness of traditionally defined herbal properties for distinguishing prescriptions of traditional Chinese medicine from non-prescription recipes. *J. Ethnopharmacol.* **2007**, *1*, 21–28. [CrossRef]

152. Chen, Z.; Cao, Y.; He, S.; Qiao, Y. Development of models for classification of action between heat-clearing herbs and blood-activating stasis-resolving herbs based on theory of traditional Chinese medicine. *Chin. Med.-UK* **2018**, *13*, 12. [CrossRef] [PubMed]

153. Unschuld, P.U. *Huang Di Nei Jing Su Wen: Nature, Knowledge, Imagery in an Ancient Chinese Medical Text: With an Appendix: The Doctrine of the Five Periods and Six Qi in the Huang Di Nei Jing Su Wen*; University of California Press: Berkeley, CA, USA, 2003.

154. Li-Ling, J. Human phenome based on Traditional Chinese Medicine—A solution to congenital syndromology. *Am. J. Chin. Med.* **2003**, *31*, 991–1000. [CrossRef]

155. Member of the Chinese Pharmacopoeia. *Pharmacopoeia of the People's Republic of China*; Subdivision of 2015 edition; China Medical Science and Technology Press: Beijing, China, 2015; pp. 274–275.

156. Ru, J.; Li, P.; Wang, J.; Zhou, W.; Li, B.; Huang, C.; Li, P.; Guo, Z.; Tao, W.; Yang, Y.; et al. TCMSP: A database of systems pharmacology for drug discovery from herbal medicines. *J. Cheminform.* **2014**, *6*, 13. [CrossRef]

157. Liu, Z.; Guo, F.; Wang, Y.; Li, C.; Zhang, X.; Li, H.; Diao, L.; Gu, J.; Wang, W.; Li, D.; et al. BATMAN-TCM: A Bioinformatics Analysis Tool for Molecular mechANism of Traditional Chinese Medicine. *Sci. Rep.-UK* **2016**, *6*, 21146. [CrossRef]

158. Zhang, R.; Yu, S.; Bai, H.; Ning, K. TCM-Mesh: The database and analytical system for network pharmacology analysis for TCM preparations. *Sci. Rep.-UK* **2017**, *7*, 2821. [CrossRef]

159. Chen, C.Y.C. TCM Database@ Taiwan: The world's largest traditional Chinese medicine database for drug screening in silico. *PLoS ONE* **2011**, *6*, e15939. [CrossRef] [PubMed]

160. O'Boyle, N.M. Towards a Universal SMILES representation-A standard method to generate canonical SMILES based on the InChI. *J. Cheminform.* **2012**, *4*, 22. [CrossRef] [PubMed]

161. Yap, C.W. PaDEL-descriptor: An open source software to calculate molecular descriptors and fingerprints. *J. Comput. Chem.* **2011**, *32*, 1466–1474. [CrossRef] [PubMed]

162. Wishart, D.S.; Feunang, Y.D.; Guo, A.C.; Lo, E.J.; Marcu, A.; Grant, J.R.; Assempour, N. DrugBank 5.0: A major update to the DrugBank database for 2018. *Nucleic Acids Res.* **2017**, *46*, D1074–D1082. [CrossRef] [PubMed]

163. Knox, C.; Law, V.; Jewison, T.; Liu, P.; Ly, S.; Frolkis, A.; Pon, A.; Banco, K.; Mak, C.; Neveu, V.; et al. DrugBank 3.0: A comprehensive resource for 'Omics' research on drugs. *Nucleic Acids Res.* **2010**, *39*, D1035–D1041. [CrossRef] [PubMed]

164. Szklarczyk, D.; Santos, A.; von Mering, C.; Jensen, L.J.; Bork, P.; Kuhn, M. STITCH 5: Augmenting protein–chemical interaction networks with tissue and affinity data. *Nucleic Acids Res.* **2016**, *44*, D380–D384. [CrossRef]

165. Gaulton, A.; Bellis, L.J.; Bento, A.P.; Chambers, J.; Davies, M.; Hersey, A.; Light, Y.; McGlinchey, S.; Michalovich, D.; Al-Lazikani, B.; et al. ChEMBL: A large-scale bioactivity database for drug discovery. *Nucleic Acids Res.* **2011**, *40*, D1100–D1107. [CrossRef]

166. Liu, T.; Lin, Y.; Wen, X.; Jorissen, R.N.; Gilson, M.K. BindingDB: A web-accessible database of experimentally determined protein–ligand binding affinities. *Nucleic Acids Res.* **2006**, *35*, D198–D201. [CrossRef]

167. Gilson, M.K.; Liu, T.; Baitaluk, M.; Nicola, G.; Hwang, L.; Chong, J. BindingDB in 2015: A public database for medicinal chemistry, computational chemistry and systems pharmacology. *Nucleic Acids Res.* **2015**, *44*, D1045–D1053. [CrossRef]

168. National Health and Family Planning Commission of PRC. Food safety national standard for use of food additives. In *GB2760—2014*; National Health and Family Planning Commission of PRC, Ed.; Beijing, China, 2014; p. 279.

169. Adams, T.B.; Cohen, S.M.; Doull, J.; Feron, V.J.; Goodman, J.I.; Marnett, L.J.; Wagner, B.M. The FEMA GRAS assessment of cinnamyl derivatives used as flavor ingredients. *Food Chem. Toxicol.* **2004**, *42*, 157–185. [CrossRef]

170. Garg, N.; Sethupathy, A.; Tuwani, R.; Dokania, S.; Iyer, A.; Gupta, A.; Badhwar, R. FlavorDB: A database of flavor molecules. *Nucleic Acids Res.* **2017**, *46*, D1210–D1216. [CrossRef] [PubMed]

171. John, R.; Owen, I.T.N.J. Visualization of Molecular Fingerprints. *J. Chem. Inf. Model.* **2011**, *51*, 1552–1563.

172. Monev, V. Introduction to similarity searching in chemistry. *MATCH Commun. Math. Comput. Chem.* **2004**, *51*, 7–38.

173. Zhu, F.; Shi, Z.; Qin, C.; Tao, L.; Liu, X.; Xu, F.; Han, B. Therapeutic target database update 2012: A resource for facilitating target-oriented drug discovery. *Nucleic Acids Res.* **2011**, *40*, D1128–D1136. [CrossRef]

174. Chen, X.; Ji, Z.L.; Chen, Y.Z. TTD: Therapeutic target database. *Nucleic Acids Res.* **2002**, *30*, 412–415. [CrossRef] [PubMed]

175. Davis, A.P.; Grondin, C.J.; Johnson, R.J.; Sciaky, D.; McMorran, R.; Wiegers, J.; Mattingly, C.J. The comparative toxicogenomics database: Update 2019. *Nucleic Acids Res.* **2018**, *47*, D948–D954. [CrossRef]

176. Kanehisa, M.; Goto, S.; Sato, Y.; Furumichi, M.; Tanabe, M. KEGG for integration and interpretation of large-scale molecular data sets. *Nucleic Acids Res.* **2011**, *40*, D109–D114. [CrossRef]

177. Huang, D.W.; Sherman, B.T.; Lempicki, R.A. Bioinformatics enrichment tools: Paths toward the comprehensive functional analysis of large gene lists. *Nucleic Acids Res.* **2009**, *37*, 1–13. [CrossRef]

178. Shannon, P.; Markiel, A.; Ozier, O.; Baliga, N.S.; Wang, J.T.; Ramage, D.; Ideker, T. Cytoscape: A software environment for integrated models of biomolecular interaction networks. *Genome Res.* **2003**, *13*, 2498–2504. [CrossRef]

179. Scardoni, G.; Petterlini, M.; Laudanna, C. Analyzing biological network parameters with CentiScaPe. *Bioinformatics* **2009**, *25*, 2857–2859. [CrossRef]