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A hybrid systems biology and systems pharmacology investigation of Zingerone's effects on reconstructed human epidermal tissues

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Abstract

Background: As individuals live longer, elderly populations can be expected to face issues. This pattern urges researchers to investigate the aging concept further to produce successful anti-aging agents. In the current study, the effects of Zingerone (a natural compound) on epidermal tissues were analyzed using a bioinformatics approach.

Methods: For this purpose, we chose the GEO dataset GSE133338 to carry out the systems biology and systems pharmacology approaches, ranging from identifying the differentially expressed genes to analyzing the gene ontology, determining similar structures of Zingerone and their features (i.e., anti-oxidant, anti-inflammatory, and skin disorders), constructing the gene–chemicals network, analyzing gene–disease relationships, and validating significant genes through the evidence presented in the literature.

Results: The post-processing of the microarray dataset identified thirteen essential genes among control and Zingerone-treated samples. The procedure revealed various structurally similar chemical and herbal compounds with possible skin-related effects. Additionally, we studied the relationships of differentially expressed genes with skin-related diseases and validated their direct connections with skin disorders the evidence available in the literature. Also, the analysis of the microarray profiling dataset revealed the critical role of interleukins as a part of the cytokines family on skin aging progress.

Conclusions: Zingerone, and potentially any constituents of Zingerone (e.g., their similar compound scan functionality), can be used as therapeutic agents in managing skin disorders such as skin aging. However, the beneficial effects of Zingerone should be assessed in other models (i.e., human or animal) in future studies.

Keywords: Zingerone, Skin-aging, Systems biology, Systems pharmacology, Interleukin, Gene–disease association, Gene–chemicals network, Similar compounds, Skin disorder

Background

The skin, consisting of the epidermis, dermis, and subcutaneous layers, is the body's largest organ and forms a physical barrier between the external environment and

the internal environment that protects and maintains. As the population ages, the epidermis and dermis are the primary targets for various changes that encourage the development of novel anti-aging therapeutic agents [1]. Physical and chemical environmental factors such as UV radiation and xenobiotics play significant roles in the oxidative stress of skin cells by altering the involved signaling pathways, immunosuppression, and producing reactive oxygen species (ROS) and photosensitivity

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diseases [2]. Various skin anti-aging treatment procedures are available, including topical retinoids, peels (e.g., salicylic acid), botulinum neurotoxin, soft tissue fillers, collagens, hyaluronic acid, autologous fat, allogenic and synthetic products, lasers, surgical procedures, and endocrinological therapies, as well as other alternatives such as phytohormones [3]. The reports showed that the use of natural compounds has promising results in reducing UV-induced effects of skin aging, which have made them play the primary role in cosmetic-related sciences [4].

Zingerone (4-(4-hydroxy-3-methoxyphenyl)-2-butanone) is an inexpensive and nontoxic phenolic alkanone structure derived from Ginger (*Zingiber officinale* Rosc.), which is a widely used herb in pharmaceutical and food industries throughout the world (e.g., China, Greece, and India) [5–7]. Zingerone is a result of gingerol dehydration while being cooked or dried [5]. The main pharmacological properties of Zingerone include anti-oxidative, immune-stimulant, anti-inflammatory, and anti-cancer effects [8]. Previous studies reported the anti-ultraviolet B (UVB) radiation activity of Zingerone in protecting the epidermis [9].

Zingerone likely acts as a neuroprotective agent by blocking the apoptotic pathway, thus preventing oxidative stress and limiting inflammation [10]. It is thought that polyphenolic compounds called Zingerone are present in ginger and have potent anti-oxidant properties, exhibit free radical scavenging activity, and provide resistance to oxidative stress [11]. Various protective effects of Zingerone have been reported in lead-induced toxicity [12], streptozotocin/high fat diet-induced type 2 diabetes [13], rheumatoid arthritis [14], lipopolysaccharide-induced oxidative stress, DNA damage, cytokine storms [15], experimental colon carcinogenesis [16], alloxan-induced oxidative stress [17], cyclophosphamide-induced organ toxicity [11], and cisplatin (cis-diamminedichloroplatinum (II))-induced jejunal toxicity [18]. Zingerone substantially decreased NF- κ B, TGF- β , TNF- α , IL-1 β , IL-6, and Hs-CRP levels while considerably increasing IL-10 levels and restoring anti-oxidant enzyme levels [14]. Thus, when given to animals (e.g., Wistar rats) exposed to the above-mentioned toxicities and diseases, Zingerone may reduce oxidative stress, inflammation, and multi-organ damage.

To the best of the authors' knowledge, no investigation has used systems biology and systems pharmacology approaches to determine significantly differentially expressed genes between control tissues and those treated by Zingerone. In this study, we used the available microarray gene expression profiling datasets to meet this aim. The functional and cellular mechanisms of identified genes were also inspected. Then, various network analyses, including gene–disease and gene–chemicals, were

performed. Finally, the effects of chemical and herbal compounds similar to Zingerone's structure were studied in detail, and the validation of potential significant genes was reviewed based on evidence found in the literature.

Methods

A summary of the current research workflow is illustrated as a flowchart diagram, as shown in Fig. 1.

Data source

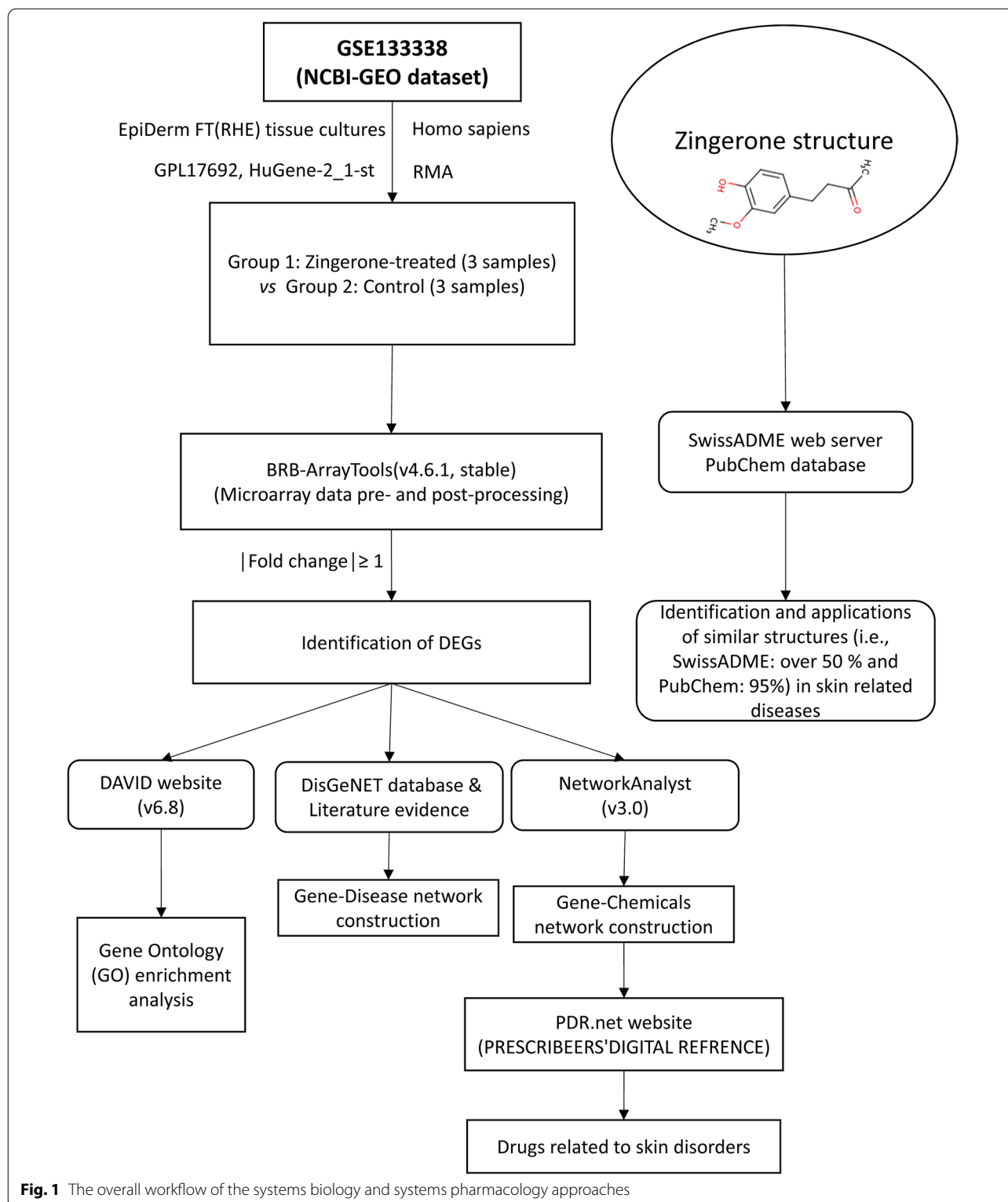
The dataset used in this study is publicly available from the gene expression omnibus (GEO) database repository of the national center for biotechnology information (NCBI) (i.e., <https://www.ncbi.nlm.nih.gov/geo/>) with the GPL17692 [HuGene-2_1-st] Affymetrix Human Gene 2.1 ST Array [transcript (gene) version] platform. The only available GEO dataset, GSE133338, included six reconstructed human epidermal (RHE) tissues treated by Zingerone (n=3) and water control (n=3), as shown in Fig. 1.

Differentially expressed genes (DEGs) between two types of tissues

Dr. Richard Simon and the BRB-ArrayTools Development Team developed a genomics analytical tool, BRB-ArrayTools (v4.6.1, stable version), to determine potent DEGs. Several steps, including GEO dataset import, gene filtering (i.e., $|\text{fold change}| \geq 1$), and normalization (i.e., quantile normalization), and annotation (i.e., “pd.hugene.2.1.st” R package [19]), were required to identify the significant DEGs. The BRB-ArrayTools used the *gcRMA* (guanine-cytosine robust multi-array analysis) algorithm to map the probe intensities into their corresponding gene expression values by discarding existing noise. The comparison between two treated groups resulted in the identification of significant DEGs using values of 10,000 and 1 for univariate permutation tests and the threshold of fold change. The obtained DEG results were significant at $p \leq 0.05$.

Gene ontology and functional enrichment analyses

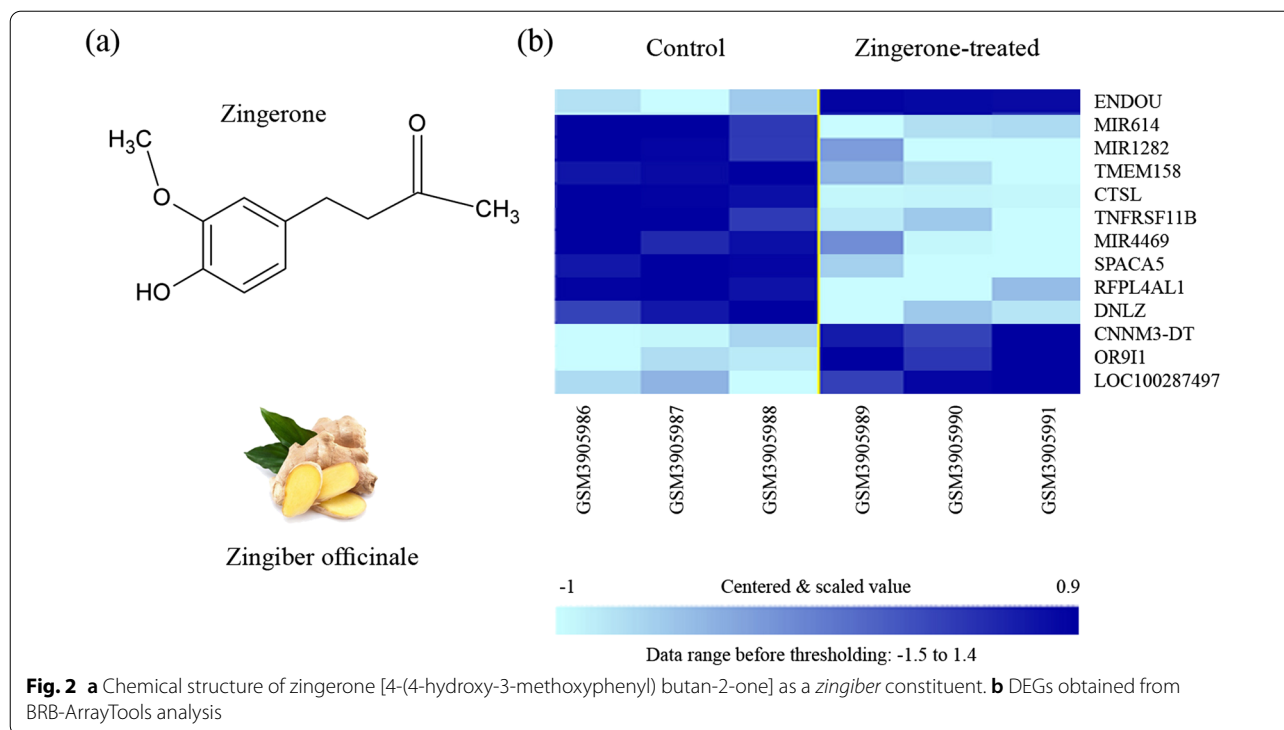
DAVID v. 6.8 (Database for Annotation, Visualization, and Integrated Discovery), which is freely available at <http://david.abcc.ncifcrf.gov/summary.jsp>, provided the evaluation of the gene ontology (GO). This evaluation included cellular components, molecular functions, and biological processes of DEGs [20, 21]. The threshold for the EASE score of a modified Fisher exact p value was set to its default value of 0.1.



Effectiveness and similarity structure analyses of Zingerone

The canonical SMILES (simplified molecular-input line-entry system) string for Zingerone structure (shown

in Fig. 2a) was obtained from the PubChem compound database (<https://pubchem.ncbi.nlm.nih.gov/compound>) [22]. Each string of SMILES was used for PubChem similarity structure and ADME prediction using online web



server tools, i.e., SwissADME [23–25], SwissSimilarity [26], and SwissTargetPrediction [27]. The SwissADME web server covers the drug design and discovery by computing several parameters, including physicochemical descriptors, ADME-related parameters, pharmacokinetic properties, drug-likeness effect, and studying medicinal chemistry friendliness of SMILES structure.

The similarity criteria for the PubChem similarity structure and the SwissSimilarity tools were 0.92 and 0.50, respectively. Finally, we screened the literature for any existing evidence for functionalities of similar compounds.

Gene–disease and gene–chemicals network analyses

We extracted the related diseases with evidence according to the significant genes obtained through the user-friendly DisGeNET (i.e., <http://www.disgenet.org/>) platform, derived from the literature on human gene–disease associations [28]. Additionally, the involvement of obtained DEGs affected by Zingerone treatment in several specific diseases (and possibly in skin-related disorders) was thoroughly screened through the literature studies to confirm and validate whether such genes are expressed as potential biomarkers of the disease. Furthermore, we constructed and analyzed the gene–chemicals network from the NetworkAnalyst 3.0 webserver to reveal potent associations between genes and compounds available in literature [29].

Results

Since missing any possible genes could affect the final results, all of the genes included in the microarray dataset are considered. The data preprocessing and class comparison approach using a two-sample t test revealed a total of sixty probe IDs, from which only thirteen DEGs were available as annotated genes. Four genes were downregulated, and nine were upregulated (as shown in Fig. 2b), along with their gene expression levels between control and Zingerone-treated samples.

The DAVID functional annotation tool revealed that two cellular components (i.e., (i) GO:0005615, and extracellular space with four involved genes TNFRSF11B, CTSL, ENDOU, and SPACA5 and (ii) GO:0005576, an extracellular region with three involved genes TNFRSF11B, CTSL, and ENDOU) were found significant. The kappa values of 1.00 and 0.80 indicated a very high level of similarity between the two GO terms. Moreover, the statistical measurement values for GO:0005615 and GO:0005576 were fold enrichments of 7.73 and 4.85, Bonferroni values of 0.09 and 0.72, Benjamini values of 0.088 and 0.60, and false discovery rate (FDR) values of 0.088 and 0.6, respectively. The detailed inspection of GO terms shows that their corresponding child terms have various relationships and cross-references with GO:0005576 and GO:0005615.

The relationships involving the extracellular space suggest that interleukin-35 complex, interleukin-27, interleukin-23,

and interleukin-12 were part of GO:0005615. Moreover, the relationships involving the extracellular region were mainly part of the extracellular isoamylase complex, extracellular ferritin complex, extracellular space, extracellular vesicle, and extracellular matrix, to mention a few.

Four types of interleukins (i.e., interleukin-1, interleukin-6, interleukin-34, and interleukin-34 alpha) had direct relationships with cross-references of GO:0005615 (for more information, refer to <https://www.ebi.ac.uk/QuickGO/GTerm?id=GO:0005615>). Several interleukin types, including interleukin-12 alpha, interleukin-23 alpha, interleukin-17, interleukin-1 alpha, interleukin-1 beta, and interleukin-6, were related to cross-references of GO:0005576 (derived from <https://www.ebi.ac.uk/QuickGO/GTerm?id=GO:0005576>).

The assessment of the absorption, distribution, metabolism, and excretion (ADME) of the Zingerone structure using the bioavailability radar (Fig. 3a) indicates the high bioactive drug-likeness property and represents the lipophilicity, molecular weight, solubility, and flexibility properties positioned in the pink area. Moreover, physicochemical and lipophilicity properties (Lipinski's rule of five) (i.e., molecular weight: 194.23 g/mol, number of rotatable bonds: 4, number of H-bond acceptors: 3, number of H-bond donors: 1, and consensus Log Po/w: 1.79) show no violations. The water solubility parameters, including Log S (ESOL), Log S (Ali), and Log S (SILICOS-IT), demonstrate very soluble, very soluble, and soluble features, respectively. Also, the pharmacokinetics properties reveal a high level of gastrointestinal absorption and only CYP1A2 inhibitory function among other cytochrome enzymes inhibitors.

The SwissTargetPrediction analysis results in a total of 100 target proteins for Zingerone, among which enzymes, secreted proteins, nuclear receptors, and oxidoreductases make up the highest percentages (Fig. 3b). A further inspection of similar structures through the SwissSimilarity and PubChem uncovered two FDA-approved drugs (i.e., Nabumetone and Masoprocol), two experimental drugs (i.e., Matairesinol and 3-(4-hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)propane-1-one), and three Zingiber constituents (i.e., 6-Shogaol, 6-Paradol, and 6-Gingerol) (listed in Table 1). The inspection also revealed their validated anti-inflammatory and anti-oxidant properties, as well as the confirmed skin disorders, such as skin anti-aging, through the evidence provided in the literature.

The gene–disease relationship outcomes from the DisGeNET (accompanied by the relevant evidence from the literature) are summarized in Table 2. The results indicate that the DEGs influence various diseases, including skin-related disorders. Furthermore, the construction of the gene–chemicals network shows the involvement of seven DEGs that are directly associated with different chemicals. Only four of them (i.e., TNFRSF11B, DNLZ, OR9I1, and MIR614) are related to twenty-three skin-related compounds (shown in Fig. 4).

Discussion

Sunlight is a source of ultraviolet (UV) radiation, which can harm the skin. Skin aging, which results from exposure to UV radiation, is often classified into three major categories (i.e., UV-A, UV-B, and UV-C). UV-A makes up 95% of the UV rays that reach the Earth's surface, and

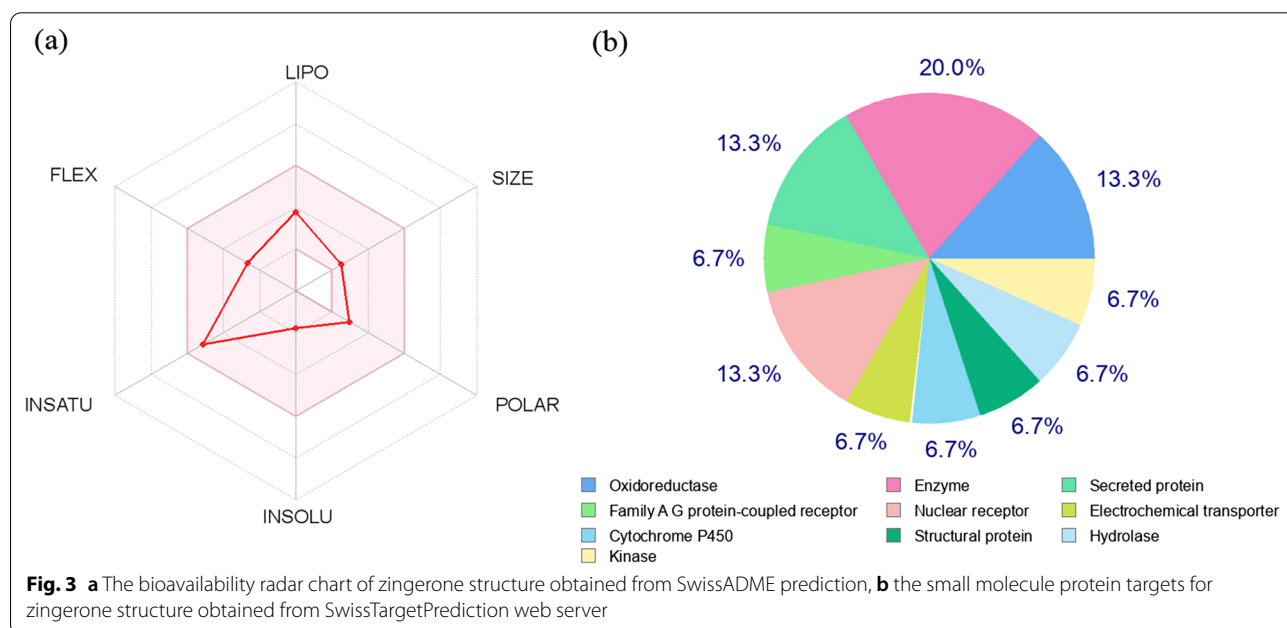


Table 1 The list of identified compounds from SwissSimilarity and PubChem structure similarity accompanied by their anti-oxidant, anti-inflammatory, and related skin disorders

Item	Compound	Similarity	Status	Antioxidant	Anti-inflammatory	Skin disorders
1	Nabumetone	0.8 ¹	FDA approved	☑ [62]	☑ [63]	Skin injury [64]
2	Masoprocol	0.672 ¹	FDA approved	☑ [65]	☑ [65]	Sun damage (actinic keratosis) [66]
3	Matairesinol	0.815 ²	Experimental	☑ [67]	☑ [68]	Skin aging [69]
4	3-(4-hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one (Phloretin)	0.726 ²	Experimental	☑ [70]	☑ [70]	Skin damage [71, 72]
5	6-Shogaol	> 0.95 ³	Zingiber constituents	☑ [73, 74]	☑ [73, 74]	Skin aging [75]
6	6-Paradol	> 0.95 ³	Zingiber constituents	☑ [76, 77]	☑ [77]	Skin cancer [76]
7	6-Gingerol	> 0.92 ³	Zingiber constituents	☑ [74]	☑ [74]	Skin aging and damage [75, 78]

¹ The obtained results are from SwissSimilarity through performing ligand-based virtual screening of combined FDA approved drugs (n = 1516) of small molecules (> 50%)

² The obtained results are from SwissSimilarity through performing ligand-based virtual screening of combined experimental drugs (n = 4788) of small molecules (> 50%)

³ The obtained results are from PubChem structure similarity through Tanimoto threshold of 95% and 92%

UV-B makes up the remaining 5% [30]. UV-C is absorbed by the ozone layer. Because of the small amount of UV-B that reaches the Earth, there is no substantial evidence, confirming that UV-B causes more damage than UV-A. UV-A and UV-B may both harm the DNA and proteins of cells [31, 32]. UV light causes reactive oxygen species (ROS) through oxidized lipids and proteins to be produced on the skin's surface. These ROS initiate oxidative stress and mutations, thus accelerating skin aging and wrinkling. UV-A primarily promotes the production of ¹O₂, whereas both UV-A and UV-B cause the production of ¹O₂⁻ via the activation of NADPH oxidase [33–35]. Exposure to UV-B radiation induces erythema by upregulating the expression of cyclooxygenase-2 (COX-2), which stimulates the inflammation process [36].

As we age, we naturally produce less collagen and other skin components, resulting in reduced collagen synthesis and enhanced collagen breakdown. This causes the appearance of skin aging associated explicitly with dermal matrix alterations that may include wrinkling, stiffness, and weakness of skin aging, as well as loss of skin elasticity [37]. Through the release of interleukins (e.g., (IL)-1a and IL-6), the ¹O₂ produced by UV-A promotes matrix metalloproteinase (MMP-1) generation in human skin fibroblasts [38, 39] and decreases collagen synthesis [40].

The effects of several anti-oxidants on the skin and skin cells, including ascorbic acid, tocopherols, carotenoids, natural compounds, and polyphenols, are of great importance [41]. These chemicals are mainly responsible for ROS and DNA damage reduction generated on the skin's surface. Among these, polyphenols are a kind of molecular structure generally extracted from plants with the structural feature of phenol units with anti-inflammatory and anti-oxidant properties. They are reported to have

COX inhibition activity, promote resistance to oxidative stress, and stop skin aging [42]. Moreover, the anti-oxidant or anti-inflammatory activities of phenolic acids can be enhanced through the presence of methoxy (-OCH₃), phenolic hydroxyl (-OH) groups, and carboxylic acid (-CH₂COOH, -CH=CHCOOH, -COOH) [43].

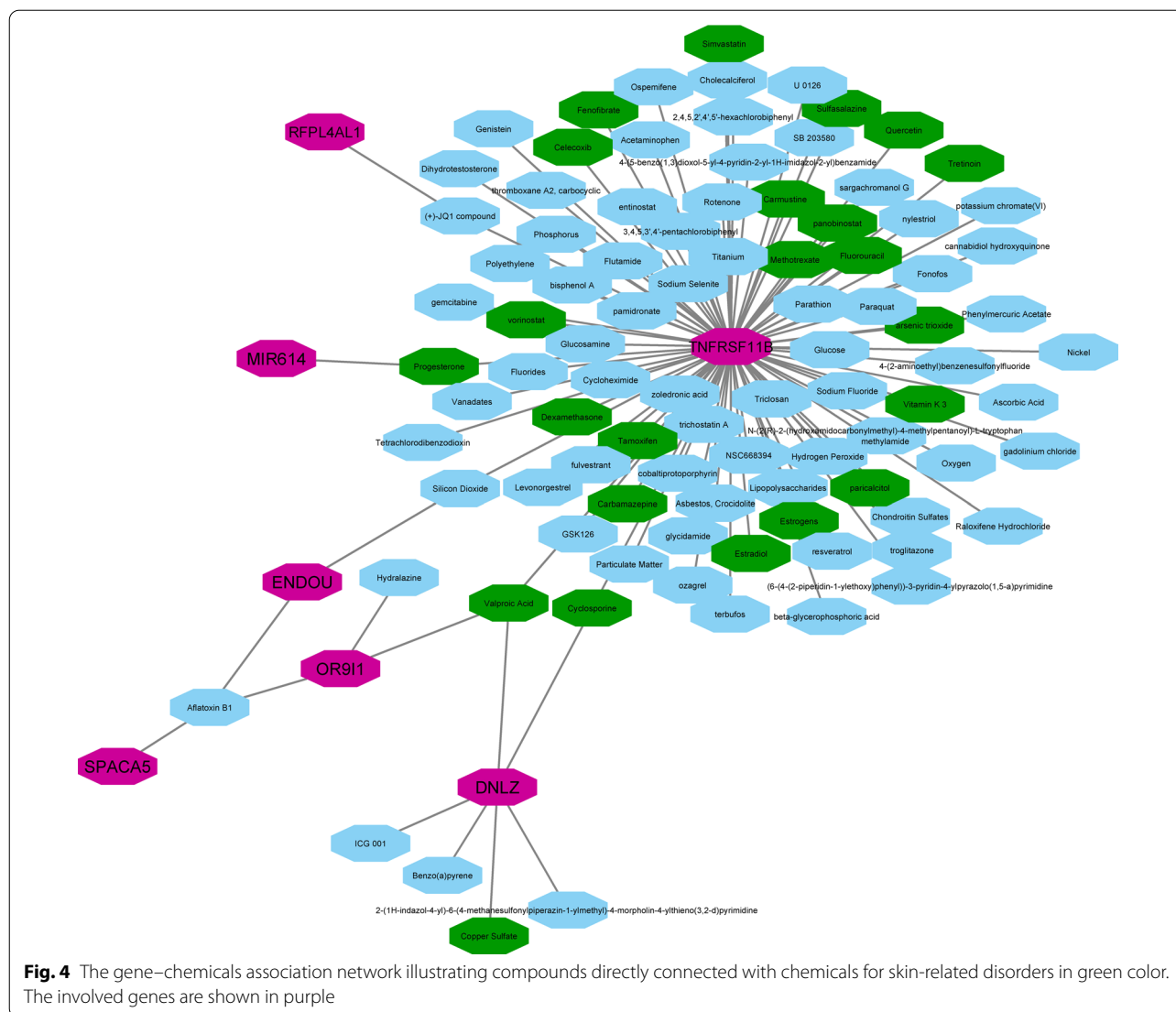
To investigate the anti-oxidant activity of the compounds, IC₅₀ values are quantitatively measured to indicate how much of a particular inhibitory chemical is used to inhibit a biological component, such as an enzyme or receptor, by fifty percent. The higher anti-oxidant activities are in direct relationship with smaller IC₅₀ values [43]. As listed in Table 3, the structures of Zingerone and similar compounds obtained from the results represent FDA-approved/experimental drugs and natural compounds. These chemicals with phenolic hydroxyl or methoxy groups automatically inherit the anti-oxidant and anti-inflammatory activities that prevent skin aging. On the other hand, their IC₅₀ values were extracted from bindingdb.org, a public database of measured binding affinities [44, 45]. The extracted pIC₅₀ = -LOG₁₀(IC₅₀) values for eight structurally similar compounds and Zingerone range from 3.8 to 4.5 in different target/enzyme environments, representing their high anti-oxidant and anti-inflammatory activities. The primary mechanism of action of these compounds in terms of their anti-oxidant features is the direct scavenging of free radicals. The radical oxidation of anti-oxidants results in a more stable, less radical reaction. By interacting with the reactive radicals, anti-oxidants stabilize the ROS.

The methoxy and hydroxyl groups of the anti-oxidants with the highest reactivity can make free radicals inactive (i.e., Eq. (1)):

Table 2 Validation of significant DEGs using DisGeNET and literature evidence for their related diseases. $\log_2|FC|$ values are derived from ExAtlas meta-analysis web server

Gene Symbols	$\log_2 FC $	DisGeNET	Literature
CTSL	1.47 ¹	Disease: Meningioma Disease Class: Neoplasms; Nervous System Diseases [79] Disease: Liver carcinoma Disease Class: Digestive System Diseases; Neoplasms [81] Disease: Hereditary Diffuse Gastric Cancer Disease Class: Digestive System Diseases; Neoplasms [83]	Skin Proteome and Degradome [80] Keratinocytes and perturbation of hair Follicle cycling [82] Mouse skin carcinogenesis [84]
RFPL4AL1 *Paralog of FPL4A gene	1.56 ¹	Disease: Malignant neoplasms Class: Neoplasms Disease: Colorectal carcinoma Class: Digestive System Diseases; Neoplasms Disease: Primary malignant neoplasm Class: Neoplasms [85]	Malignant melanoma [86] COVID-19 disease [87] Hepatocellular carcinoma [88]
TNFRSF11B	1.62 ¹	Disease: Hyperphosphatasemia with bone disease Disease Class: Musculoskeletal Diseases [89] Disease: Osteoporosis Disease Class: Nutritional and Metabolic Diseases; Musculoskeletal Diseases [91] Disease: Rheumatoid Arthritis Disease Class: Skin and Connective Tissue Diseases; Musculoskeletal Diseases; Immune System Diseases [93]	Skin inflammation [90] Skeletal dysplasias [92]
SPACA5	1.64 ¹	No matches found	Bladder cancer [94]
TMEM158	1.88 ¹	Disease: Neoplasms [95] Disease: Carcinogenesis Disease Class: Pathological Conditions, Signs, and Symptoms; Neoplasms [97] Disease: Ovarian neoplasm Disease Class: Neoplasms; Female Urogenital Diseases and Pregnancy Complications; Endocrine System Diseases [98]	Pediatric localized scleroderma skin [96] Anaplastic large cell lymphoma [97] Skin [99]
DNLZ	1.93 ¹	Disease: Neoplasms [100] Disease: Liver carcinoma Disease Class: Digestive System Diseases; Neoplasms [102] Disease: Tumor cell invasion [104]	Immune evasion [101] Fibrogenic responses [103] Psoriasis [105]
MIR614	2.00 ¹	Disease: ovarian neoplasm; malignant neoplasm of ovary; carcinoma, ovarian epithelial Disease Class: Neoplasms; Female Urogenital Diseases and Pregnancy Complications; Endocrine System Diseases [106]	Psoriasis [107] Suppression of stromal interferon signaling [108]
MIR1282	2.00 ¹	No matches found	Breast cancers [109] Hepatocellular carcinoma [110] Associated with immune organs and immunocytes [111]
MIR4469	2.58 ¹	Disease: Malignant neoplasm of breast; breast carcinoma Disease Class: Neoplasms; Skin and Connective Tissue Diseases [112]	Atherosclerosis [113] Laryngeal carcinoma cells [114]
LOC100287497 (SEPTIN7P13)	0.50 ²	No matches found	Hepatocellular carcinoma [114] Urinary bladder cancer [115]
OR9I1	0.59 ²	No matches found	Human keratinocytes [116]
CNNM3-DT	0.60 ²	Disease: Rheumatoid arthritis Disease Class: Skin and Connective Tissue Diseases; Musculoskeletal Diseases; Immune System Diseases [117]	Lipid metabolism [118]
ENDOU	0.61 ²	Disease: Mental depression Disease Class: Behavior Mechanisms [119] Disease: Depressive disorder Disease Class: Mental Disorders [121] Disease: Depressed mood Disease Class: Behavior and Behavior Mechanisms [122]	Skin diseases [120]

¹ Upregulated DEGs² Downregulated DEGs



where R[·] is a type of free radical such as hydroxyl, peroxy, alkoxy, or alkyl radicals and O[·] or OCH₂[·] are the remained free radicals [46, 47]. Similarly, the mechanism of action of these chemicals, given their anti-inflammatory properties, applies through radical scavenging activities [48].

Additionally, it has been established that the immune system can function in the human body as a double-edged sword in which immunity and immunopathology simultaneously provide benefits and do damage by balancing innate and adaptive immunity [49]. In a recent review, Zouboulis et al. stated that “In clinical practice, ‘to look better’ does not mean to ‘look younger.’” [50].

Skin, the largest organ of the human body, inherits all immune system functions for better studying inflammation, autoimmunity, and cancer [51]. Skin aging is a multistep process that can be promoted through sun exposure, which may result in epidermal changes and photo-aging [52]. Various studies have proposed the benefits of natural compounds such as curcumin and its analogs in treating skin disorders such as skin aging [53, 54].

In the current investigation, the effects of Zingerone on epidermal tissues have been studied while considering the differentially expressed genes and the cellular components involved. As an outcome, without any exceptions, the assessed genes play roles in involving interleukins,

Table 3 Structure activity relationships of similar compounds and their targets/enzymes

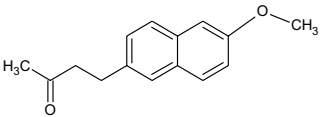
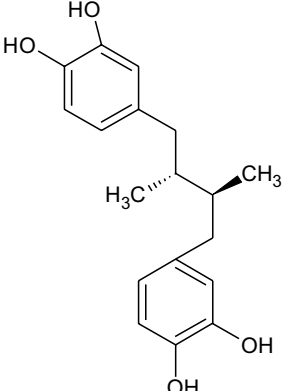
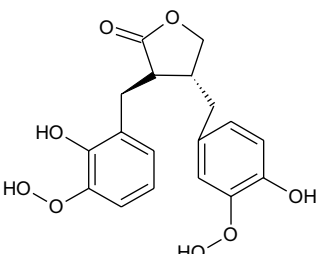
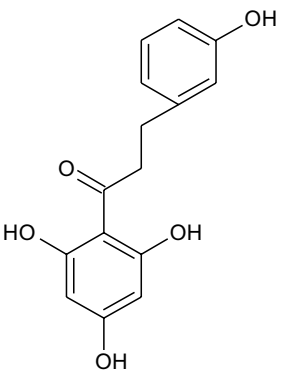
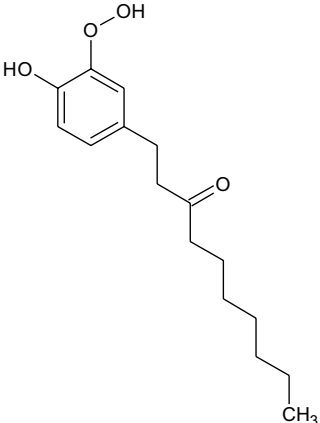
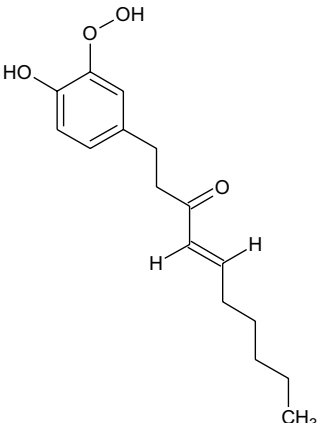
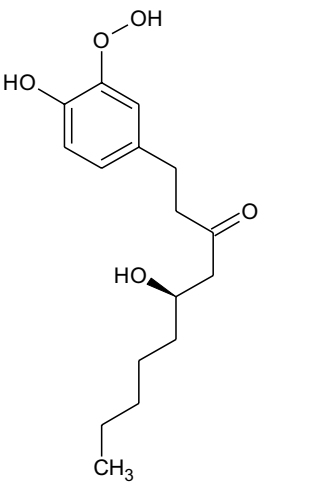
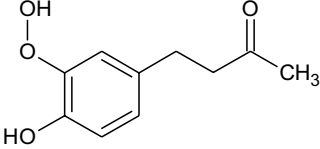
Compound	Structure	IC50 (nM) (BindingDB.org)	Target/enzyme from DrugBank and literature	
			Target	Enzyme
Nabumetone		> 5.00E + 4 Estrogen receptor	Prostaglandin G/H synthase 2 [123] [124] Prostaglandin G/H synthase 1 [125, 126]	Myeloperoxidase [127]
Masoprocol		> 5.00E + 4 Androgen receptor	Arachidonate 5-lipoxygenase [128] [129] Sex hormone-binding globulin [130]	Arachidonate 5-lipoxygenase [131]
Matairesinol		5.20E + 4 Testis-specific androgen-binding protein	Dehydrogenase/reductase SDR family member 4-like 2 [132]	N/A
3-(4-hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one (Phloretin)		1.67E + 5 Topoisomerase I/II	HTH-type transcriptional regulator TtgR [132]	N/A

Table 3 (continued)

Compound	Structure	IC50 (nM) (BindingDB.org)	Target/enzyme from DrugBank and literature	
			Target	Enzyme
6-Paradol		> 3.00E + 4 Cytochrome P450 3A	Pain receptor [133]	COX1 [133] Capsaicin [133]
6-Shogaol		9.96E + 4 Cytochrome P450 2E1	Prostaglandin E [134] NF-κB [135]	Phase II genes expression enzymes [136]
6-Gingerol		1.29E + 5 Cyclooxygenase-1 (COX-1)	Cell growth regulatory proteins [135] NF-κB [135]	COX-2 [137] Extracellular signal- regulated kinases (ERK) [135]
Zingerone		1.53E + 5 Androgen Receptor	Peroxisome proliferator-acti- vated receptor alpha [138]	Xanthine oxidase [8] Acetyl-CoA car- boxylase [138] Acetyl-CoA syn- thetase [138]

which are a well-known group of cytokines expressed mainly by leukocytes. Cytokines, which are produced by the Langerhans cells of the skin's immune system, were reported to play a significant role in skin aging [55]. Based on the identified differentially expressed genes and their effective cellular components in terms of GO, including GO:0005615 and GO:0005576, eighteen and four types of interleukins were determined to play roles in extracellular space and region, respectively.

In line with our results, Shirato et al. found that ETAS 50 could prevent skin aging by decreasing both UV-B-induced IL-6 and IL-1 beta expressions (56, 57). Also, Guo et al. reported that adipose-derived stem cells could secrete several interleukins (e.g., interleukin-1 β , interleukin-8, interleukin-9, interleukin-12, interleukin-15, and interleukin-17) to inhibit skin aging [58]. Exercising could also affect interleukin-15 levels, thus preventing skin aging [59]. Interleukin 17 (or IL-17A) has a direct relationship with the stimulation of IL-23, making them a golden IL-23/IL-17 axis in age-associated inflammation and attenuates skin aging via acetyl Zingerone treatment through IL-17A stimulation [60, 61].

In summary, the current study proposed a hybrid systems biology and systems pharmacology procedure to identify the functional mechanisms and successful effects of Zingerone treatment. The proposed procedure considers the impact of similar compounds for stimulating the involved interleukins family on skin aging and their antioxidant and anti-inflammatory properties. More experimental studies on human and animal models are required to confirm the present results, as Zingerone's effects on cellular and molecular mechanisms on skin aging are still unclear.

Conclusions

The prominent role of herbal remedies is clear to the research and scientific communities. Skin aging and other types of skin disorders have attracted the attention of people throughout the world. In this regard, several drugs and chemicals have been proposed for anti-aging purposes. In this study, a computational and statistical procedure was considered to investigate the effect of Zingerone on skin aging at the cellular and genomic levels. Additionally, compounds that are structurally similar to Zingerone and their impacts on skin-related diseases were studied.

Furthermore, the gene–disease association and gene–chemicals network analyses revealed undeniable direct connections between genetics and skin disorders, including skin aging. Finally, various types of interleukins were found to have vital roles in attenuating skin aging. However, further research using human or animal models is

required to confirm the effects of Zingerone determined in the present study.

Abbreviations

DEG: Differentially expressed genes; GEO: Gene expression omnibus; GO: Gene ontology; KEGG: Kyoto encyclopedia of genes and genomes; NCBI: National Center for Biotechnology Information; RHE: Reconstructed human epidermal; SMILES: Simplified Molecular Input Line Entry System; FDA: Food and Drug Administration (US); ADME: Absorption, distribution, metabolism, and excretion; CTSL: Cathepsin L; RFPL4AL1: Ret Finger Protein Like 4A Like 1; TNFRSF11B: TNF Receptor Superfamily Member 11b; SPACA5: Sperm Acrosome Associated 5; TMEM158: Transmembrane Protein 158; DNLZ: DNL-Type Zinc Finger; MIR614: MicroRNA 614; MIR1282: MicroRNA 1282; MIR4469: MicroRNA 4469; LOC100287497 (SEPTIN7P13): Septin 7 Pseudogene 13; OR9I1: Olfactory Receptor Family 9 Subfamily I Member 1; CNNM3-DT: CNNM3 Divergent Transcript; ENDOU: Endonuclease, Poly(U) Specific; UV: Ultraviolet radiation; ROS: Reactive oxygen species; NADPH: Nicotinamide adenine dinucleotide phosphate.

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Authors' contributions

BS and SA were involved in conceptualization and supervision; EA, BS, and SA helped in data curation, methodology, roles/writing—original draft and writing—review and editing; EA and SA—contributed to formal analysis; EA and BS were involved in investigation; BS—project administration; All authors read and approved the final manuscript.

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The authors declare that they have no competing interest.

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References

- Rosenthal A, Jacoby T, Israilevich R, Moy R (2019) The role of bioidentical hormone replacement therapy in anti-aging medicine: a review of the literature. *Int J Dermatol*. Online ahead of print
- Bickers DR, Athar M (2006) Oxidative stress in the pathogenesis of skin disease. *J Invest Dermatol* 126(12):2565–2575
- Sator PG (2006) Skin treatments and dermatological procedures to promote youthful skin. *Clin Interv Aging* 1(1):51
- Dunaway S, Odin R, Zhou L, Ji L, Zhang Y, Kadekar AL (2018) Natural antioxidants: multiple mechanisms to protect skin from solar radiation. *Front Pharmacol* 9:392
- Choi J-S, Ryu J, Bae W-Y, Park A, Nam S, Kim J-E et al (2018) Zingerone suppresses tumor development through decreasing cyclin D1 expression and inducing mitotic arrest. *Int J Mol Sci* 19(9):2832
- Kandemir FM, Yildirim S, Kucukler S, Caglayan C, Mahamadu A, Dortbudak MB (2018) Therapeutic efficacy of zingerone against

- vancomycin-induced oxidative stress, inflammation, apoptosis and aquaporin 1 permeability in rat kidney. *Biomed Pharmacother* 105:981–991
7. Mani V, Arivalagan S, Siddique AI, Namasivayam N (2016) Antioxidant and anti-inflammatory role of zingerone in ethanol-induced hepatotoxicity. *Mol Cell Biochem* 421(1–2):169–181
 8. Ahmad B, Rehman MU, Amin I, Arif A, Rasool S, Bhat SA et al (2015) A review on pharmacological properties of zingerone (4-(4-Hydroxy-3-methoxyphenyl)-2-butanone). *Sci World J* 2015:816364
 9. Lee J, Oh SW, Shin SW, Lee K-W, Cho J-Y, Lee J (2018) Zingerone protects keratinocyte stem cells from UVB-induced damage. *Chem Biol Interact* 279:27–33
 10. Rashid S, Wali AF, Rashid SM, Alsaffar RM, Ahmad A, Jan BL, et al (2021) Zingerone Targets status epilepticus by blocking hippocampal neurodegeneration via regulation of redox imbalance, inflammation and apoptosis. *Pharmaceuticals (Basel)* 14(2)
 11. Mir B, Amin I, Rehman M, Razak R, Ali A, Baba O et al (2018) Chemo-protective potential of zingerone (vanillyl acetone) in cyclophosphamide-induced hepatic toxicity. *Pharmacogn Mag* 14(57):434–439
 12. Amin I, Hussain I, Rehman MU, Mir BA, Ganaie SA, Ahmad SB et al (2021) Zingerone prevents lead-induced toxicity in liver and kidney tissues by regulating the oxidative damage in Wistar rats. *J Food Biochem* 45(3):e13241
 13. Rehman MU, Rashid SM, Rasool S, Shakeel S, Ahmad B, Ahmad SB et al (2019) Zingerone (4-(4-hydroxy-3-methylphenyl)butan-2-one) ameliorates renal function via controlling oxidative burst and inflammation in experimental diabetic nephropathy. *Arch Physiol Biochem* 125(3):201–209
 14. Bashir N, Ahmad SB, Rehman MU, Muzamil S, Bhat RR, Mir MUR et al (2021) Zingerone (4-(four-hydroxy-3-methylphenyl) butane-two-1) modulates adjuvant-induced rheumatoid arthritis by regulating inflammatory cytokines and antioxidants. *Redox Rep Commun Free Radic Res* 26(1):62–70
 15. Wali AF, Rehman MU, Raish M, Kazi M, Rao PGM, Alnemer O, et al (2020) Zingerone [4-(3-methoxy-4-hydroxyphenyl)-butan-2] attenuates lipopolysaccharide-induced inflammation and protects rats from sepsis associated multi organ damage. *Molecules* 25(21)
 16. Ganaie MA, Al Saeedan A, Madhkali H, Jan BL, Khatlani T, Sheikh IA et al (2019) Chemopreventive efficacy zingerone (4-[4-hydroxy-3-methylphenyl] butan-2-one) in experimental colon carcinogenesis in Wistar rats. *Environ Toxicol* 34(5):610–625
 17. Ahmad B, Rehman MU, Amin I, Mir MUR, Ahmad SB, Farooq A et al (2018) Zingerone (4-(4-hydroxy-3-methylphenyl) butan-2-one) protects against alloxan-induced diabetes via alleviation of oxidative stress and inflammation: probable role of NF- κ B activation. *Saudi Pharm J* 26(8):1137–1145
 18. Rehman MU, Ahmad B, Arif A, Rasool S, Farooq A, Razaq R et al (2015) Zingerone protects against cisplatin-induced oxidative damage in the jejunum of Wistar rats. *Orient Pharm Exp Med* 15(3):199–206
 19. Carvalho B. pd.hugene.2.1.st: Platform Design Info for Affymetrix HuGene-2_1-st. R package version 3.14.1. <https://www.bioconductor.org/> 2015:1–2
 20. da Huang W, Sherman BT, Lempicki RA (2009) Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc* 4(1):44–57
 21. da Huang W, Sherman BT, Lempicki RA (2009) Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists. *Nucleic Acids Res* 37(1):1–13
 22. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S et al (2021) PubChem in 2021: new data content and improved web interfaces. *Nucleic Acids Res* 49(D1):D1388–D1395
 23. Daina A, Michielin O, Zoete V (2014) iLOGP: a simple, robust, and efficient description of n-octanol/water partition coefficient for drug design using the GB/SA approach. *J Chem Inf Model* 54(12):3284–3301
 24. Daina A, Michielin O, Zoete V (2017) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep* 7:42717
 25. Daina A, Zoete V (2016) A boiled-egg to predict gastrointestinal absorption and brain penetration of small molecules. *ChemMedChem* 11(11):1117–1121
 26. Zoete V, Daina A, Bovigny C, Michielin O (2016) SwissSimilarity: a web tool for low to ultra high throughput ligand-based virtual screening. *J Chem Inf Model* 56(8):1399–1404
 27. Gfeller D, Michielin O, Zoete V (2013) Shaping the interaction landscape of bioactive molecules. *Bioinformatics* 29(23):3073–3079
 28. Piñero J, Ramírez-Anguaita JM, Saúch-Pitarch J, Ronzano F, Centeno E, Sanz F et al (2020) The DisGeNET knowledge platform for disease genomics: 2019 update. *NAR* 48(D1):D845–D855
 29. Xia J, Gill EE, Hancock REW (2015) NetworkAnalyst for statistical, visual and network-based meta-analysis of gene expression data. *Nat Protoc* 10(6):823–844
 30. Jallad KN (2017) Chemical characterization of sunscreens composition and its related potential adverse health effects. *J Cosmet Dermatol* 16(3):353–357
 31. Ikehata H (2018) Mechanistic considerations on the wavelength-dependent variations of UVR genotoxicity and mutagenesis in skin: the discrimination of UVA-signature from UV-signature mutation. *Photochem Photobiol Sci* 17(12):1861–1871
 32. Browne N, Donovan F, Murray P, Saha S (2014) Cyanobacteria as bio-factories for production of UV-screening compounds. *OA Biotechnol* 3(6)
 33. Cadet J, Sage E, Douki T (2005) Ultraviolet radiation-mediated damage to cellular DNA. *Mutat Res/Fundam Mol Mech Mutagen* 571(1–2):3–17
 34. Subedi L, Lee TH, Wahedi HM, Baek S-H, Kim SY (2017) Resveratrol-enriched rice attenuates UVB-ROS-induced skin aging via downregulation of inflammatory cascades. *Oxid Med Cell Longev*. 2017
 35. Valencia A, Kochevar IE (2008) Nox1-based NADPH oxidase is the major source of UVA-induced reactive oxygen species in human keratinocytes. *J Investig Dermatol* 128(1):214–222
 36. Rhodes LE, Gledhill K, Masoodi M, Haylett AK, Brownrigg M, Thody AJ et al (2009) The sunburn response in human skin is characterized by sequential eicosanoid profiles that may mediate its early and late phases. *FASEB J* 23(11):3947–3956
 37. Hwang K-A, Yi B-R, Choi K-C (2011) Molecular mechanisms and in vivo mouse models of skin aging associated with dermal matrix alterations. *Lar* 27(1):1–8
 38. Scharffetter-Kochanek K, Wlaschek M, Briviva K, Sies H (1993) Singlet oxygen induces collagenase expression in human skin fibroblasts. *FEBS Lett* 331(3):304–306
 39. Wlaschek M, Heinen G, Poswig A, Schwarz A, Krieg T, Scharffetter-Kochanek K (1994) UVA-induced autocrine stimulation of fibroblast-derived collagenase/MMP-1 by interrelated loops of interleukin-1 and interleukin-6. *Photochem Photobiol* 59(5):550–556
 40. Tanaka H, Okada T, Konishi H, Tsuji T (1993) The effect of reactive oxygen species on the biosynthesis of collagen and glycosaminoglycans in cultured human dermal fibroblasts. *Arch Dermatol Res* 285(6):352–355
 41. Masaki H (2010) Role of antioxidants in the skin: anti-aging effects. *J Dermatol Sci* 58(2):85–90
 42. Lee JY, Jang YW, Kang HS, Moon H, Sim SS, Kim CJ (2006) Anti-inflammatory action of phenolic compounds from *Gastrodia elata* root. *Arch Pharm Res* 29(10):849–858
 43. Chen J, Yang J, Ma L, Li J, Shahzad N, Kim CK (2020) Structure-antioxidant activity relationship of methoxy, phenolic hydroxyl, and carboxylic acid groups of phenolic acids. *Sci Rep* 10(1):2611
 44. Liu T, Lin Y, Wen X, Jorissen RN, Gilson MK (2007) BindingDB: a web-accessible database of experimentally determined protein–ligand binding affinities. *NAR* 35(suppl_1):D198–D201
 45. Gilson MK, Liu T, Baitaluk M, Nicola G, Hwang L, Chong J (2016) BindingDB in 2015: a public database for medicinal chemistry, computational chemistry and systems pharmacology. *NAR* 44(D1):D1045–D1053
 46. Krinsky NI (1992) Mechanism of action of biological antioxidants. *PSEBM* 200(2):248–254
 47. Nijveldt RJ, Van Nood E, Van Hoorn DE, Boelens PG, Van Norren K, Van Leeuwen PA (2001) Flavonoids: a review of probable mechanisms of action and potential applications. *Am J Clin Nutr* 74(4):418–425
 48. Hussain T, Tan B, Yin Y, Blachier F, Tossou MCB, Rahu N (2016) Oxidative stress and inflammation: What polyphenols can do for us? *Oxid Med Cell Longev* 2016:7432797
 49. Musa M (2013) Immune mechanism: a “double-edged sword.” *Malays J Med Sci* 20(3):61–67

50. Zouboulis CC, Ganceviciene R, Liakou AI, Theodoridis A, Elewa R, Makrantonaki E (2019) Aesthetic aspects of skin aging, prevention, and local treatment. *Clin Dermatol* 37(4):365–372
51. Matejuk A (2018) Skin immunity. *Arch Immunol Ther Exp* 66(1):45–54
52. Bennett MF, Robinson MK, Baron ED, Cooper KD (2008) Skin immune systems and inflammation: protector of the skin or promoter of aging? *J Invest Dermatol Proc* 13(1):15–19
53. Panahi Y, Fazlollahzadeh O, Atkin SL, Majeed M, Butler AE, Johnston TP et al (2019) Evidence of curcumin and curcumin analogue effects in skin diseases: a narrative review. *J Cell Physiol* 234(2):1165–1178
54. Vollono L, Falconi M, Gaziano R, Iacovelli F, Dika E, Terracciano C et al (2019) Potential of curcumin in skin disorders. *Nutrients* 11(9):2169
55. Borg M, Brincat S, Camilleri G, Schembri-Wismayer P, Brincat M, Calleja-Agius J (2013) The role of cytokines in skin aging. *Climacteric* 16(5):514–521
56. Shirato K, Koda T, Takanari J, Sakurai T, Ogasawara J, Imaizumi K et al (2018) Anti-inflammatory effect of ETAS[®] 50 by inhibiting nuclear factor- κ B p65 nuclear import in ultraviolet-B-irradiated normal human dermal fibroblasts. *Evid Based Complement Altern Med* 2018:5072986
57. Shirato K, Koda T, Takanari J, Ogasawara J, Sakurai T, Ohno H et al (2018) ETAS[®] 50 attenuates ultraviolet-B-induced interleukin-6 expression by suppressing Akt phosphorylation in normal human dermal fibroblasts. *Evid Based Complement Altern Med* 2018:1547120
58. Guo J, Pijun Y, Wang L, Shi Y, Liu Y, Chen W (2017) Research progress and application outlook of paracrine functions of adipose-derived stem cells in facial anti-aging. *Chin J Tissue Eng Res* 38(5):789–794
59. Crane JD, MacNeil LG, Lally JS, Ford RJ, Bujak AL, Brar IK et al (2015) Exercise-stimulated interleukin-15 is controlled by AMPK and regulates skin metabolism and aging. *Aging Cell* 14(4):625–634
60. Swindell WR, Bojanowski K, Chaudhuri RK (2019) A Zingerone Analog, Acetyl Zingerone, bolsters matrix synthesis, inhibits matrix metalloproteinases, and represses IL-17A target gene expression. *J Invest Dermatol* 140(3):602–614
61. Mohammadi Shahrokhi V, Ravari A, Mirzaei T, Zare-Bidaki M, Asadikaram G, Arababadi MK (2018) IL-17A and IL-23: plausible risk factors to induce age-associated inflammation in Alzheimer's disease. *Immunol Investig* 47(8):812–822
62. Essawy SS (2011) Comparative study of the effect of allopurinol and nabumetone either alone or combined on Freund's adjuvant-induced arthritis in rats. *Med J Cairo Univ* 79(2)
63. Barth A, Kaiser N, Löffler U, Sourgens H, Klinger W (1994) Influence of the xanthine derivative denbutylline and the anti-inflammatory agent nabumetone on microsomal free radical production and lipid peroxidation in rat liver. *Exp Toxicol Pathol* 46(6):483–489
64. Jenner PN (1987) Nabumetone in the treatment of skin and soft tissue injury. *Am J Med* 83(4):101–106
65. Matsunami K (2018) Frailty and *Caenorhabditis elegans* as a benchtop animal model for screening drugs including natural herbs. *Front Nutr* 5:111
66. Olsen EA, Abernethy ML, Kulp-Shorten C, Callen JP, Glazer SD, Huntley A et al (1991) A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. *J Am Acad Dermatol* 24(5):738–743
67. Yamauchi S, Sugahara T, Nakashima Y, Okada A, Akiyama K, Kishida T et al (2006) Radical and superoxide scavenging activities of matairesinol and oxidized matairesinol. *Biosci Biotechnol Biochem* 70(8):1934–1940
68. Xu P, Huang M-W, Xiao C-X, Long F, Wang Y, Liu S-Y et al (2017) Matairesinol suppresses neuroinflammation and migration associated with Src and ERK1/2-NF- κ B pathway in activating BV2 microglia. *Neurochem Res* 42(10):2850–2860
69. Kim M-J, Kim J-Y, Jung T-K, Choi S-W, Yoon K-S (2006) Skin anti-aging effect of *Forsythia viridissima* L. extract. *KSBB J* 21(6):444–450
70. Behzad S, Sureda A, Barreca D, Nabavi SF, Rastrelli L, Nabavi SM (2017) Health effects of phloretin: from chemistry to medicine. *Phytochem Rev* 16(3):527–533
71. Oresajo C, Stephens T, Hino PD, Law RM, Yatskayer M, Foltis P et al (2008) Protective effects of a topical antioxidant mixture containing vitamin C, ferulic acid, and phloretin against ultraviolet-induced photo-damage in human skin. *J Cosmet Dermatol* 7(4):290–297
72. Shin S, Kum H, Ryu D, Kim M, Jung E, Park D (2014) Protective effects of a new phloretin derivative against UVB-induced damage in skin cell model and human volunteers. *Int J Mol Sci* 15(10):18919–18940
73. Li F, Nitteranon V, Tang X, Liang J, Zhang G, Parkin KL et al (2012) In vitro antioxidant and anti-inflammatory activities of 1-dehydro-[6]-gingerdione, 6-shogaol, 6-dehydroshogaol and hexahydrocurcumin. *Food Chem* 135(2):332–337
74. Dugasani S, Pichika MR, Nadarajah VD, Balijepalli MK, Tandra S, Korlakunta JN (2010) Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol. *J Ethnopharmacol* 127(2):515–520
75. Han HS, Kim KB, Jung JH, An IS, Kim Y-J, An S (2018) Anti-apoptotic, antioxidant and anti-aging effects of 6-shogaol on human dermal fibroblasts. *Biomed Dermatol* 2(1):1–8
76. Chung W-Y, Jung Y-J, Surh Y-J, Lee S-S, Park K-K (2001) Antioxidative and antitumor promoting effects of [6]-paradol and its homologs. *Mutat Res/Genet Toxicol Environ Mutagen* 496(1–2):199–206
77. Sapkota A, Park SJ, Choi JW (2019) Neuroprotective effects of 6-shogaol and its metabolite, 6-paradol, in a mouse model of multiple sclerosis. *Biomol Ther (Seoul)* 27(2):152
78. Kim J-K, Kim Y, Na K-M, Surh Y-J, Kim T-Y (2007) [6]-Gingerol prevents UVB-induced ROS production and COX-2 expression in vitro and in vivo. *Free Rad Res* 41(5):603–614
79. Lah TT, Nanni I, Trinkaus M, Metellus P, Dussert C, De Ridder L et al (2010) Toward understanding recurrent meningioma: the potential role of lysosomal cysteine proteases and their inhibitors. *J Neurosurg* 112(5):940–950
80. Tholen S, Biniossek ML, Gansz M, Gomez-Auli A, Bengsch F, Noel A et al (2013) Deletion of cysteine cathepsins B or L yields differential impacts on murine skin proteome and degradome. *Mol Cell Proteom* 12(3):611–625
81. Ruan J, Zheng H, Fu W, Zhao P, Su N, Luo R (2014) Increased expression of cathepsin L: a novel independent prognostic marker of worse outcome in hepatocellular carcinoma patients. *PLoS ONE* 9(11):e112136
82. Roth W, Deussing J, Botchkarev VA, Pauly-Evers M, Saftig P, Hafner A et al (2000) Cathepsin L deficiency as molecular defect of furless: hyperproliferation of keratinocytes and perturbation of hair follicle cycling. *FASEB J* 14(13):2075–2086
83. Yamashita S, Tsujino Y, Moriguchi K, Tatematsu M, Ushijima T (2006) Chemical genomic screening for methylation-silenced genes in gastric cancer cell lines using 5-aza-2'-deoxycytidine treatment and oligonucleotide microarray. *Cancer Sci* 97(1):64–71
84. Benavides F, Perez C, Blando J, Contreras O, Shen J, Coussens LM et al (2012) Protective role of cathepsin L in mouse skin carcinogenesis. *Mol Carcinog* 51(4):352–361
85. Naito A, Yamamoto H, Kagawa Y, Naito Y, Okuzaki D, Otani K et al (2015) RFPL4A increases the G1 population and decreases sensitivity to chemotherapy in human colorectal cancer cells. *J Biol Chem* 290(10):6326–6337
86. Gil J, Kim Y, Szeitz B, Doma V, Çakir U, de Almeida NP, et al (2021) Proteogenomics reveals how metastatic melanoma modulates the immune system to allow immune evasion. *bioRxiv*. 2021:2021.04.10.439245
87. Hunter E, Koutsothanasi C, Wilson A, Santos FC, Salter M, Westra JW, et al (2020) Development and validation of blood-based prognostic biomarkers for severity of COVID disease outcome using Episwitch 3D genomic regulatory immuno-genetic profiling. *medRxiv*. 2021:2021.06.21.21259145
88. Hu Z, Huang P, Yan Y, Zhou Z, Wang J, Wu G (2019) Hepatitis B virus X protein related lncRNA WEE2-AS1 promotes hepatocellular carcinoma proliferation and invasion. *Biochem Biophys Res Commun* 508(1):79–86
89. Naot D, Wilson LC, Allgrove J, Adviento E, Picc I, Musson DS et al (2020) Juvenile Paget's disease with compound heterozygous mutations in TNFRSF11B presenting with recurrent clavicular fractures and a mild skeletal phenotype. *Bone* 130:115098
90. Laggner M, Copic D, Nemeč L, Vorstandlechner V, Gugerell A, Gruber F et al (2020) Therapeutic potential of lipids obtained from γ -irradiated PBMCs in dendritic cell-mediated skin inflammation. *EBioMedicine* 55:102774
91. Fallahnezhad S, Jajarmi V, Shahnava S, Amini A, Ghoreishi SK, Kazemi M et al (2020) Improvement in viability and mineralization of osteoporotic bone marrow mesenchymal stem cell through combined application

- of photobiomodulation therapy and oxytocin. *Lasers Med Sci* 35(3):557–566
92. Hellemans J (2007) Identification and analysis of genes involved in skeletal dysplasias affecting growth and bone homeostasis. Ghent University
 93. Chen Y, Li H, Luo X, Liu H, Zhong Y, Wu X et al (2019) Moxibustion of Zusanli (ST36) and Shenshu (BL23) alleviates cartilage degradation through RANKL/OPG signaling in a rabbit model of rheumatoid arthritis. *Evid Based Complement Altern Med* 2019:6436420
 94. Zhang XY, Yan QX, Guo XY, Chen CR, Chen RQ, Cai ZM et al (2016) Expression profile of SPACA5/Spaca5 in spermatogenesis and transitional cell carcinoma of the bladder. *Oncol Lett* 12(5):3731–3738
 95. Fu Y, Yao N, Ding D, Zhang X, Liu H, Ma L et al (2020) TMEM158 promotes pancreatic cancer aggressiveness by activation of TGFβ1 and PI3K/AKT signaling pathway. *J Cell Physiol* 235(3):2761–2775
 96. Mirizio E, Liu C, Yan Q, Waltermire J, Mandel R, Schollaert KL et al (2021) Genetic signatures from RNA sequencing of pediatric localized scleroderma skin. *Front Pediatr* 9:669116
 97. Liu L, Zhang J, Li S, Yin L, Tai J (2020) Silencing of TMEM158 inhibits tumorigenesis and multidrug resistance in colorectal cancer. *Nutr Cancer* 72(4):662–671
 98. Cheng Z, Guo J, Chen L, Luo N, Yang W, Qu X (2015) Overexpression of TMEM158 contributes to ovarian carcinogenesis. *J Exp Clin Cancer Res* 34(1):75
 99. Lulli D, Carbone ML, Pastore S (2016) Epidermal growth factor receptor inhibitors trigger a type I interferon response in human skin. *Oncotarget* 7(30):47777–47793
 100. Vezenkova LT, Tsekova DS, Kostadinova I, Mihaylova R, Vassilev NG, Danchev ND (2019) Synthesis of new galanthamine-peptide derivatives designed for prevention and treatment of Alzheimer's disease. *Curr Alzheimer Res* 16(3):183–192
 101. Boyd A, Bennuru S, Wang Y, Sanprasert V, Law M, Chaussabel D et al (2013) Quiescent innate response to infective filariae by human Langerhans cells suggests a strategy of immune evasion. *Infect Immun* 81(5):1420–1429
 102. He L, Cai X, Cheng S, Zhou H, Zhang Z, Ren J et al (2019) Ornithine transcarbamylase downregulation is associated with poor prognosis in hepatocellular carcinoma. *Oncol Lett* 17(6):5030–5038
 103. Fang F, Shanguan AJ, Kelly K, Wei J, Gruner K, Ye B et al (2013) Early growth response 3 (Egr-3) is induced by transforming growth factor-β and regulates fibrogenic responses. *Am J Pathol* 183(4):1197–1208
 104. Ju A, Cho YC, Kim BR, Lee S, Le HTT, Vuong HL et al (2018) Anticancer effects of methanol extract of *Myrmecodia platytyrea* Becc. leaves against human hepatocellular carcinoma cells via inhibition of ERK and STAT3 signaling pathways. *Int J Oncol* 52(1):201–210
 105. Müller A (2020) The Central Role of the Transcriptional Regulator I [kappa] B [zeta] in Psoriasis: Eberhard Karls Universität Tübingen
 106. Zhang J, Gao D, Zhang H (2018) Upregulation of miR-614 promotes proliferation and inhibits apoptosis in ovarian cancer by suppressing PPP2R2A expression. *Mol Med Rep* 17(5):6285–6292
 107. Ekman AK, Vegfors J, Eding CB, Enerbäck C (2017) Overexpression of Psoriasin (S100A7) contributes to dysregulated differentiation in psoriasis. *Acta Derm Venereol* 97(4):441–448
 108. Raikhy G, Woodby BL, Scott ML, Shin G, Myers JE, Scott RS, et al (2019) Suppression of stromal interferon signaling by human papillomavirus 16. *J Virol* 93(19)
 109. Qian P, Banerjee A, Wu ZS, Zhang X, Wang H, Pandey V et al (2012) Loss of SNAIL regulated miR-128-2 on chromosome 3p22.3 targets multiple stem cell factors to promote transformation of mammary epithelial cells. *Cancer Res* 72(22):6036–6050
 110. Zhuang L, Xu L, Wang P, Meng Z (2015) Serum miR-128-2 serves as a prognostic marker for patients with hepatocellular carcinoma. *PLoS ONE* 10(2):e0117274
 111. Yang Y, Xu J, Chen H, Fei X, Tang Y, Yan Y et al (2016) MiR-128-2 inhibits common lymphoid progenitors from developing into progenitor B cells. *Oncotarget* 7(14):17520–17531
 112. Cao T, Xiao T, Huang G, Xu Y, Zhu JJ, Wang K et al (2017) CDK3, target of miR-4469, suppresses breast cancer metastasis via inhibiting Wnt/β-catenin pathway. *Oncotarget* 8(49):84917–84927
 113. Sleptsov AA, Nazarenko MS, Lebedev IN, Skriabin NA, Frolov AV, Popov VA et al (2014) Somatic genome variations in vascular tissues and peripheral blood leukocytes in patients with atherosclerosis. *Genetika* 50(8):986–995
 114. Xue HX, Li HF, Wang T, Li WJ, Bian WC (2020) LncRNA HCG11 suppresses laryngeal carcinoma cells progression via sponging miR-4469/APOM axis. *Eur Rev Med Pharmacol Sci* 24(6):3174–3182
 115. Nascimento e Pontes MG, da Silveira SM, Trindade Filho JC, Rogatto SR, Viana de Camargo JL (2013) Chromosomal imbalances in successive moments of human bladder urothelial carcinoma. *Urol Oncol* 31(6):827–835
 116. Kang W, Son B, Park S, Choi D, Park T (2021) UV-irradiation- and inflammation-induced skin barrier dysfunction is associated with the expression of olfactory receptor genes in human keratinocytes. *Int J Mol Sci* 22(6)
 117. Lu MC, Yu HC, Yu CL, Huang HB, Koo M, Tung CH et al (2016) Increased expression of long noncoding RNAs LOC100652951 and LOC100506036 in T cells from patients with rheumatoid arthritis facilitates the inflammatory responses. *Immunol Res* 64(2):576–583
 118. Muret K, Désert C, Lagoutte L, Boutin M, Gondret F, Zerjal T et al (2019) Long noncoding RNAs in lipid metabolism: literature review and conservation analysis across species. *BMC Genom* 20(1):882
 119. Liu G, Wang Y, Zheng W, Cheng H, Zhou R (2019) P11 loss-of-function is associated with decreased cell proliferation and neurobehavioral disorders in mice. *Int J Biol Sci* 15(7):1383–1395
 120. Edqvist PH, Fagerberg L, Hallström BM, Danielsson A, Edlund K, Uhlén M et al (2015) Expression of human skin-specific genes defined by transcriptomics and antibody-based profiling. *J Histochem Cytochem* 63(2):129–141
 121. Gandhi M, Bhatt P, Chauhan G, Gupta S, Misra A, Mashru R (2019) IGF-II-conjugated nanocarrier for brain-targeted delivery of p11 gene for depression. *AAPS PharmSciTech* 20(2):50
 122. van Calker D, Serchov T, Normann C, Biber K (2018) Recent insights into antidepressant therapy: distinct pathways and potential common mechanisms in the treatment of depressive syndromes. *Neurosci Biobehav Rev* 88:63–72
 123. Fackovcova D, Kristova V, Kriska M (2000) Renal damage induced by the treatment with non-opioid analgesics—theoretical assumption or clinical significance. *Bratisl Lek Listy* 101(8):417–422
 124. Roy HK, Karolski WJ, Ratashak A (2001) Distal bowel selectivity in the chemoprevention of experimental colon carcinogenesis by the non-steroidal anti-inflammatory drug nabumetone. *Int J Cancer* 92(4):609–615
 125. Giuliano F, Ferraz JG, Pereira R, de Nucci G, Warner TD (2001) Cyclooxygenase selectivity of non-steroid anti-inflammatory drugs in humans: ex vivo evaluation. *Eur J Pharmacol* 426(1–2):95–103
 126. Takeuchi K, Smale S, Premchand P, Maiden L, Sherwood R, Thjodleifsson B et al (2006) Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 4(2):196–202
 127. Saleh TS, Calixto JB, Medeiros YS (1999) Effects of anti-inflammatory drugs upon nitrate and myeloperoxidase levels in the mouse pleurisy induced by carrageenan. *Peptides* 20(8):949–956
 128. Audouin C, Mestdagh N, Lassoie MA, Houssin R, Hélichart JP (2001) N-Aminoindoline derivatives as inhibitors of 5-lipoxygenase. *Bioorg Med Chem Lett* 11(6):845–848
 129. Lambert JD, Meyers RO, Timmermann BN, Dorr RT (2001) Pharmacokinetic analysis by high-performance liquid chromatography of intravenous nordihydroguaiaretic acid in the mouse. *J Chromatogr B Biomed Sci Appl* 754(1):85–90
 130. Hong H, Branham WS, Ng HW, Moland CL, Dial SL, Fang H et al (2015) Human sex hormone-binding globulin binding affinities of 125 structurally diverse chemicals and comparison with their binding to androgen receptor, estrogen receptor, and α-fetoprotein. *Toxicol Sci* 143(2):333–348
 131. Wang B, Yu SC, Jiang JY, Porter GW, Zhao LT, Wang Z et al (2011) An inhibitor of arachidonate 5-lipoxygenase, Nordy, induces differentiation and inhibits self-renewal of glioma stem-like cells. *Stem Cell Rev Rep* 7(2):458–470
 132. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H et al (2000) The protein data bank. *Nucleic Acids Res* 28(1):235–242

133. Fajrin FA, Rahmayanti F, Pratoko DK. The binding prediction of 6-paradol and its derivatives on TRPV1 agonist as a new compound for treating painful diabetic neuropathy. *Journal ILMU DASAR*. 2020(2):133–8%V 21
134. Eren D, Betul YM (2016) Revealing the effect of 6-gingerol, 6-shogaol and curcumin on mPGES-1, GSK-3 β and β -catenin pathway in A549 cell line. *Chem Biol Interact* 258:257–265
135. Prasad S, Tyagi AK (2015) Ginger and its constituents: role in prevention and treatment of gastrointestinal cancer. *Gastroenterol Res Pract* 2015:142
136. Peng S, Yao J, Liu Y, Duan D, Zhang X, Fang J (2015) Activation of Nrf2 target enzymes conferring protection against oxidative stress in PC12 cells by ginger principal constituent 6-shogaol. *Food Funct* 6(8):2813–2823
137. Kim SO, Kundu JK, Shin YK, Park JH, Cho MH, Kim TY et al (2005) [6]-Gingerol inhibits COX-2 expression by blocking the activation of p38 MAP kinase and NF-kappaB in phorbol ester-stimulated mouse skin. *Oncogene* 24(15):2558–2567
138. Geng X, Liu H, Yuwen Q, Wang J, Zhang S, Zhang X, et al. Protective effects of zingerone on high cholesterol diet-induced atherosclerosis through lipid regulatory signaling pathway. *Human & experimental toxicology*. 2021:9603271211006170

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