Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 13, Issue 3, 2023, 260
https://doi.org/10.33263/BRIAC133.260

Ginger Compress Therapy – A Painless Solution for Kidney Failure Patients

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Scopus Author ID: 7003264215
Received: 15.12.2021; Accepted: 12.01.2022; Published: 11.06.2022

Abstract: Chronic kidney disease (CKD) is one of the most outgrowing diseases of all, and globally, about 10% of the world's population is affected. Chronic kidney disease (CKD) occurs when the kidney can no longer perform its function to full capacity. There are currently two treatment options for CKD: dialysis and transplantation. Both existing treatment options have their demerits, including high cost, pain, sleep disturbances, restlessness, graft rejection, and much more. *Zingiber officinale*, also commonly known as ginger, is one of the most commonly used household herbs and a potential medicinal herb. It contains various phytochemicals such as essential oils, phenolic compounds, alkaloids, glycosides, flavonoids, terpenoids, saponin, tannin, protein, and carbohydrates. Ginger has been reported for multiple medicinal properties such as antibacterial, antioxidant, anti-inflammatory, immune-modulatory, anti-hypertensive, anti-arthritic, hepatoprotective, and nephroprotective. The nephroprotective properties of ginger are less explored than their other therapeutic properties. Few research data suggest that the aqueous extracts of ginger lowered blood glucose, serum, urea, and creatinine levels in diabetic-induced rats. It also helped to restore the changes in the kidney due to toxicity. Thus, it protects renal tissues from structural damage caused by hypoglycemia, inhibits cholesterol absorption due to oxidative stress, and also boosts the kidney's defense mechanism. The *in silico* work performed on 64 phytochemicals against the Vitamin D3 receptor target protein of CKD showed the binding efficiency of phytochemicals against this target. Diterpene (Lactone) has shown a better binding score with optimal ADMET properties. Ginger compress therapy is a very simple treatment process, using pieces of ginger boiled in hot water, after which a towel is soaked in this ginger water and spread over the lower portion of the patient's back for around 30 minutes. After this, the area must be rubbed with a few drops of gingelly oil. Currently, many Siddha and Ayurveda practitioners in India and many other countries use this therapy to cure numerous patients. Deeper research into this therapy could enhance efficiency and provide a scientific approach.

Keywords: chronic kidney disease; ginger; nephroprotective; massage therapy; *Zingiber officinale*.

1. Chronic Kidney Disease – A Global Concern

The kidney is a vital organ in the human body that filters about 150 quarts of blood to produce 1.5-2 quarts of urine that compose of waste and extra fluid [1]. Kidney disease or renal disease is a collective term used to represent any damage in the kidney that reduces its function [2]. Chronic kidney disease (CKD) occurs when the kidney can no longer function at full capacity [3]. CKD is one of the most outgrowings of all; globally, one in ten people is said to

suffer from kidney disease [4]. There are five stages in CKD. In stage 1 > 90% of the kidney functions normally; in stage 2, there is a mild decrease in the function of the kidney (50-85%), and in stage 3 mild to moderate decrease in kidney function (30-59%), in stage 4 severe decrease in kidney function were glomerular filtration rate drops up to 15-29 mL/min. In the end-stage, the kidney almost loses its functionality [5]. The treatment of CKD varies depending upon the cause of kidney loss and the underlining complication accompanied by the disease. End-stage kidney failure is treated either by dialysis or kidney transplant [6].

The Global Burden of Disease study ranked CKD in the 18th place [7], and about 10% of the world's population is affected by CKD [8]. According to WHO, high-income countries spend about 2-3% of their health care budget on the treatment of end-stage CKD, resulting in a heavy economic burden [9]. In contrast, low-income countries cannot meet the CKD treatment expenses [10]. Around the globe, 2 million people are receiving treatments for CKD [11]. Most of the patients are from the US, Japan, Germany, Italy, and Brazil. It has been estimated that CKD cases will soon increase in developing countries like India and China [12]. CKD at the early stages may be accompanied by certain signs and symptoms, including high blood pressure, changes in urination, chest pain, the softness of breath, etc. [13]. These symptoms are often non-specific and could be due to other illnesses as well. Since our kidneys are highly adaptable, they can compensate for the loss of function [14]. Kidney failure can also be due to several conditions or causes, which include type I or type II diabetes, high blood pressure, polycystic kidney diseases, and pyelonephritis [15].

2. Causes of Kidney Failure

Chronic Kidney Disease (CKD) is caused due to multiple diseases or conditions [16] which is represented in Figure 1.

Figure 1. Various causes linked to Chronic Kidney Disease.

2.1. Diabetes mellitus.

Diabetes mellitus (DM) is a leading cause of chronic renal failure [17]. DM is a health condition in which an increase in blood glucose level will clog the kidney's tiny blood vessels,

resulting in impaired function [18]. Kidney failure caused due to diabetes is termed Diabetic Kidney Disease (DKD) or Diabetic Nephropathy (DN). DN is defined based on the level of proteinuria > 0.5g/24 h [19] and is also characterized by an increase in albuminuria and a decrease in glomerular filtration rate [20]. This condition is always followed by a decrease in afferent arteriole resistance. As afferent arteriole resistance decreases, efferent arteriole resistance increases. Hence, the disease development is accompanied by structural changes in the kidney, such as renal hypertrophy, enlarged glomerular capillaries, thick ECM, and functional changes [21]. The development and progression of DKD affect the organ's cellular nature and physiological conditions [22]. Due to the physiological changes, the glomerular podocyte structure also changes. Change in podocyte structure increases the albumin concentration in urine [23]. Activation of Renin–Angiotensin–Aldosterone System (RAAS), polyol- and Advanced Glycation End product (AGE)-dependent pathways, the hexosamine pathway flux, Protein Kinase C (PKC), Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidases under the above conditions will significantly affect the homeostatic condition [24]. Because of the altered pathways, overproduction of Reactive Oxygen Species (ROS) takes place. ROS production could be due to the up-regulation of pro-oxidant enzyme-linked ROS production and a decrease in antioxidants. NOX (NADPH oxidase) also plays a major role in ROS production [25]. Excess production of ROS results in renal fibrosis, inflammation, damage by lipid peroxidation, DNA damage, and mitochondrial dysfunction [26].

2.2. Hypertension.

Hypertension and kidney go hand-in-hand. Hypertension is a long-term medical condition in which the blood pressure constantly increases in the arteries [27]. The kidney is very sensitive to arterial pressure changes [28]. Change in blood pressure subsequently leads to renal failure. A relatively small increment in arterial pressure affects the kidney [29]. Hence the normal functioning of the kidney gets affected; as a result, fluid and electrolyte balance gets altered to maintain normal circulatory homeostasis [30]. As a result, there will be an increase in urine flow along with sodium excretion. In response to high blood pressure,-natriuresis gets altered to maintain sodium excretion and sustain renal perfusion pressure [31]. Nephrons in the kidney are connected with a network of tiny hair-like capillaries called arteries [32]. Due to high blood pressure, arteries around the kidney gets narrowed or weakened [33]. This results in the nephrons stopping receiving the essential oxygen and nutrients, leading to a decrease in glomerular filtration rate, and eventually, the kidney loses its ability to filter blood [34]. The kidney also produces a hormone called aldosterone, which regulates blood pressure [35]. As negative feedback is due to kidney damage, it cannot produce aldosterone, and blood pressure keeps increasing [36].

2.3. Pyelonephritis.

Pyelonephritis is a condition of inflammation of the kidney due to bacterial infection. Various microorganisms that infect the urinary tract could be the causative agents of pyelonephritis [37]. Compared to males, females are more prone to pyelonephritis because of shorter ureters, hormonal changes, and the proximity of the urethra to the anus [38]. Escherichia coli is one of the most predominant uropathogen (80%) isolated from patients [39] and is called uropathogenic *E. coli* (UPEC). Generally, *E. coli* is a part of the normal flora of the

gastrointestinal tract. These harmless bacteria become pathogenic under immunosuppressed conditions or when gastrointestinal barriers are violated [40]. When UPEC reaches the urinary tract, they colonize and get attached to the urethral walls using their fimbriae or pili. These fimbriae or pili will react with the host receptors and cause bacterial attachment on the surface of the bladder [41]. E. coli can replicate against host defense mechanisms, finally causing acute pyelonephritis [42]. Other microbial pathogens include *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and many species of Enterobacter and Proteus. Unlike *E. coli* these organisms adopt a different mechanism of pathogenesis. Initially, these bacteria get attached to the urothelial cells of the urinary tract [43]. Urease, an enzyme produced by these organisms, will catalyze the urea in the urine and produce ammonia and carbon-di-oxide, which increases the urine's pH, leading to bladder or kidney stones. These organisms colonized in the urinary tract will move towards the bladder, causing cystitis [44]. Under untreatable conditions, these pathogens will assent via ureters to the kidney, causing acute pyelonephritis secondary infection. This condition has a high risk of irreversible kidney damage, finally leading to kidney failure [45].

2.4. Inflammation.

Inflammation is said to be an essential part of chronic kidney disease (CKD) [46]. In recent years, due to the exponential growth in the number of cases of CKD and end-stage renal disease (ESRD), inflammation is also considered a strong risk factor leading to morbidity and mortality [47]. Persistent inflammation in a CKD patient leads to not only cardiovascular risk but also atherosclerosis, protein-energy wasting (PAW), hypo-albuminemia, and malnutrition-inflammation-cachexia syndrome (MICS) [48]. Inflammatory cytokines cause anorexia via brain influence which may be directly associated with CKD [49]. Inflammation also increases resting energy expenditure and suppresses anabolic hormones like testosterone, growth hormone, and IGF1 [50]. Anemia and erythropoietin resistance (Epo) are two important factors caused by inflammation in CKD [51]. The Epo resistance due to inflammation leads to a decline in Epo production, a decrease in erythropoietin stimulatory activity, and disturbance in iron metabolism due to high levels of hepcidin [52]. Various factors contribute to CKD, such as a decrease in clearance and increase in production of pro-inflammatory cytokines, oxidative stress, acidosis, vitamin deficiency, frequent infections, altered metabolism of adipose tissue, and intestinal dysbiosis [53]. Evidence indicates a direct correlation between inflammation and glomerular filtration rate (GFR) [54]. The pathophysiology of inflammation in individuals differs due to racial, ethnic, and genetic differences. Carbonyl stress and uremic milieu-induced oxidative stress were the major pro-inflammatory agents [55]. Dialysis patients were frequently prone to infections like catheter-related blood stream infection, access site infection, thrombosed IV fistulas, etc., creating additional inflammatory stimulations [56]. A number of external factors induce inflammation in dialysis patients, like contamination of dialysis water, inadequate quality of dialysate, and bio-incompatible factors [57]. Inflammatory cytokines are produced by various tissues, which lead to the dysfunctioning of the kidney [58]. The uremic toxins cause intestinal dysbiosis, which leads to the translocation of gut bacteria and its components into the blood circulation, which again leads to systemic activation of inflammation [59].

2.5. Reactive oxygen species.

Free radicals are unstable atoms with unpaired electrons. They usually have high energy and borrow electrons from neighboring atoms in order to become stable. High concentrations of free radicals or reactive oxygen species (ROS) are injurious to health and can cause damage to the cells. ROS will normally be produced by our body's metabolism [60]. ROS production under normal conditions will be deactivated by the cellular defense mechanism. This will be accompanied by the balance between pro-oxidant and antioxidant systems. ROS production will increase if this balance is lost, leading to lipid peroxidation, protein denaturation, and DNA damage [61]. This process and certain systemic diseases will affect the kidney's normal functioning [62]. The systemic diseases include diabetes, hyperglycemia, hypertension, immunosuppressant, obesity, pyelonephritis, etc. In diabetes, this process has been explained by the glomerular hyper-filtration hypothesis [63]. Diabetes increases the glomerular filtration rate (GFR), eventually increasing the glomerular pressure that damages the cells. To stabilize this condition, angiotensin II will be secreted [64]. The auto-oxidation reaction accumulates Advanced Glycosylation End-Products (AGEP) that promote more oxygen free radicals, damaging the kidney. Another systemic condition is hypertension [65]. Hypertension or an increase in blood pressure is one of the major reasons for renal failure. Secondary hypertension results in hypo-perfusion and atherosclerosis which are directly involved in increased oxygen species (OS) and inflammation leading to stenotic kidney and kidney failure [66].

2.6. Drug toxicity.

Drug-induced nephrotoxicity is one of the complications due to several medications. The drug-induced nephrotoxicity leads to electrolyte imbalance, urine sediment abnormalities, acid-base abnormalities, hematuria decline in glomerular filtration rate, proteinuria, and pyuria [67]. About 8-60% of acquired kidney injuries are attributed to drug-induced nephrotoxicity [68]. It also acts as a source of morbidity and mortality. There are more than 10 types of toxicity and their associated drugs. Hemodynamically-mediated kidney injury is caused by drugs blocking angiotensin and angiotensin-converting enzymes [69]. This decreases renal blood flow, intra-glomerular pressure, vasoconstriction, and vasodilation. Tubular epithelial cell damage is because of direct toxic effects of drugs or ischemia effects. This causes tubular necrosis, cellular degeneration, and collapse of proximal and distal tubular basement membrane [70]. The drugs like mannitol, dextran, and radiographic contrast media cause a decline in renal function due to swelling vacuolization of proximal epithelial cells. Acute allergic interstitial nephritis is dose-dependent toxicity that causes granulomas and necrosis of epithelial cells in the kidney. The drug which causes acute interstitial nephritis is penicillin, ciprofloxacin, loop diuretics, etc. [71]. Papillary necrosis is a condition in which excess consumption of analgesic-containing phenacetin causes necrosis of renal papillae [72]. Glomerular injury is a very rare condition that may be caused due to drugs like ampicillin, rifampin, and phenytoin. It causes glomerular sclerosis with interstitial inflammation and fibrosis. Intra-tubular obstruction is caused due to intra-tubular precipitation of degenerated products, drugs, and other metabolites [73]. Anuric kidney injury develops rapidly in this condition, and urine pH decreases to 4.5. Drug-induced nephrolithiasis may be due to abnormal precipitation of crystals in the renal collection tubule, causing pain, infection, urinary tract obstruction, and kidney injury [74]. It is believed that triamterene or its metabolized initiate stone formation, and sulfadiazine

derivatives cause kidney injury and nephrolithiasis. The drugs like ciprofloxacin, amoxicillin, pseudoephedrine, and nitrofurantoin cause nephrolithiasis.

2.7. Other causes.

Other than these technical causes, poverty, pollution, and contamination also contribute to the onset of several kidney disorders leading to CKD. These factors, along with a growing population with conditions like diabetes and hypertension, could contribute to an increased number of CKD patients. It has been estimated that in 2030 India will have the largest diabetic population [75]. Despite this sobering situation, there are only 1850 nephrologists available for the 1.3 billion population, and they are concentrated in urban centers. Hence, instant screening and treatment methodologies are essential for CKD [76].

3. Issues with Existing Treatment Options of CKD

At present, there are two treatments for CKD are available, namely dialysis and transplantation:

3.1. Dialysis.

Dialysis is when the metabolic wastes are removed from the body to re-establish the normal fluid and metabolic balance. Around 130,000 people are obtaining dialysis every day, and the count is increasing. Normally it is a day-long process that takes about 30-40 minutes and must be repeated 4-5 times daily. Dialysis helps prevent the accumulation of waste products in the blood. There are three types of dialysis, namely hemodialysis (HD), peritoneal dialysis (PD), and continuous renal replacement therapy (CRRT) and all these three types of dialysis have lots of problems associated with them, and they are presented in Figure 2.

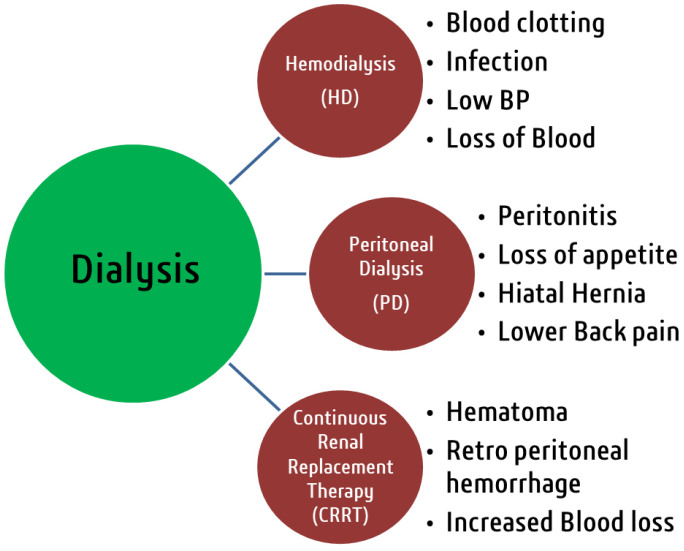


Figure 2. Types of dialysis and their common side effects.

Hemodialysis uses diffusion, osmosis, or ultrafiltration as its principle to remove toxins and extra cellular fluids from the blood [77]. Almost 120,000 patients need HD, and the cost ranges from $9 to $45. Complications associated with HD are vascular access failure, blood clotting and infection at the site, sleep disturbances, shortness of breath, muscular craps, lowering of blood pressure, etc. [78]. Peritoneal dialysis is a continuous waste removal process.

It relies on the peritoneal membrane, a permanent silicone implant catheter [79]. Two to three liters of dialysate are introduced into the abdominal cavity, and dialysis occurs through diffusion and osmosis in the implant for several hours. The dialysate must be drained and refilled 4-5 times daily. PD causes peritonitis, an inflammation caused in the inner walls of the abdomen by fungi or bacteria. Untreated peritonitis may cause rapid blood sepsis and multiple organ failure, possibly leading to death. The other problems associated with PD are leakage around the catheter insertion sites, aggravation of hiatal hernia, lower back pain, loss of appetite, and weight gain. It may be ineffective upon prolonged usage [80]. Despite these complications, 8,500 patients are going for PD regularly.

Continuous Renal Replacement Therapy (CRRT) is a special health care initiative introduced in 2017. CRRT is used to treat hemodynamically unbalanced patients in ICU. This treatment is done four times a week and is also time-consuming. Although CRRT has higher hemodynamic stability, metabolic clearance, and volume control, it brings more complications and is considered less effective. It may lead to arterio-venous fistulas, formation of hematomas, and thrombus at the site of vascular access [81]. It also causes retro peritoneal hemorrhage and air embolism. Blood recirculation through the catheter causes hemo concentration, filter clotting, and turns down filter clearance. Extended exposure to the filter membrane may cause activation of immune mediators. Frequent filter clotting may result in increased blood loss, inadequate dialysis, and loss of anti-coagulant activity [82]. About 90% of the patients are undergoing RRT, but most of them quit the treatment due to financial reasons leading to an increase in mortality.

3.2. Renal transplantation.

The other treatment for CKD is renal transplantation. Though it is believed that renal transplantation increases the life expectancy of the patients, the process gets delayed due to various factors, most importantly, getting a proper donor and financial issues. If the donor has a serum creatinine level at the time of transplantation or if he is above 60 years old, there are higher chances of renal failure [83]. Moreover, other urological and vascular complications associated with the kidney transplant may also lead to a higher risk of morbidity and mortality, as mentioned in Figure 3.

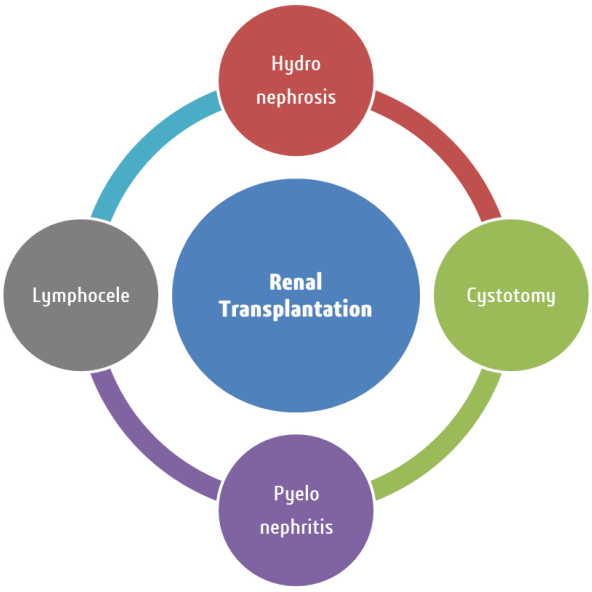


Figure 3. Common urological and vascular complications associated with kidney transplantation.

Vascular complications, including renal artery stenosis, arterial-venous fistulas, and pseudoaneurysm, and non-vascular complications like urine leak, ureteral obstruction, neoplasm, and herniation may also complicate the transplantation procedure. Financial aid, higher initial expenses, and lower availability of donors are other barriers [84]. Urological complications like hemorrhage, urinary fistulas, and acute obstruction are common after transplantation. In a few patients, distal edges of the ureter become necrotic, and urinoma occurs after 4-10 days of surgery. Later complications like hydronephrosis, lymphocele compression, cystotomic wounds, chronic pyelonephritis, and callus formation may also occur [85]. These complications may worsen the condition that a re-operation has to be done to remove fistulas, change the urinary path due to acute rejections and infections, or the graft itself has to be removed [86]. The survival rate of kidney transplant patients has been significantly lowered due to cardiovascular diseases (CVD). About 70-80% of renal transplant patients have a risk of CVD. Factors like stroke, extracranial cerebrovascular atherosclerosis, and acute coronary syndrome are the most commonly seen complications in transplanted patients. Generally, conditions like hypertension, proteinuria, diabetes, anemia, graft dis-functioning, obesity, and hyperhomo-cystenimia, increase the chance of CVD in renal transplant recipients [87]. Novel factors like oxidative stress, lupus anti-coagulant antibody systemic inflammation, and advanced glycosylation end products (AGES) contribute to the pathogenesis of CVD. High pulse pressure and left ventricular hypertrophy may even lead to the patient's morbidity [88].

Patients with diabetes and CKD undergo either sequential kidney and pancreas transplants or simultaneous pancreas and kidney transplants done in a single operation. Each of these methods has its advantages and also complications. Patients are exposed to more infections and sometimes require longer hospitalization or frequent re-admissions; this also leads to re-operation. Other complications like allograft loss, cytomegalo virus (CMV) infections, thrombosis, symptomatic lymphocele, hypoglycemia, and ketoacidosis may increase the chance of mortality. After a kidney and pancreas transplant, the survival rate depends upon the severity of the complication and age [89].

Morton et al. described the view of patients, their difficulties, and suffering due to the treatment of stage 5 CKD. The difficulties expressed by the patients include confinement, family burden, pain, time commitment, dialysis access, self-care, etc. [90]. Generally, patients with CKD have poor physical health, depression, high anxiety, anemia, metabolic acidosis, sleeplessness, fatigue, and weakness. These factors may also increase the chance of heart disease.

4. Research on New Drug for CKD

Though various treatment modalities for CKD are currently being pursued, such as the use of Angiotensin-Converting Enzyme (ACE) inhibitors, mineralocorticoid receptor antagonists, Sodium/Glucose cotransporter 2 (SGLT2) inhibitors, Endothelin Receptor Type A antagonists (ETRA), their success rate remains limited [91]. Some patients use alternate medicines or traditional medicines for their betterment. Each region in the world has its traditional practices and herbs for treating various diseases. Traditional Chinese medicine uses Astragalus membranaceus to reduce oxidative stress in the kidney cells by suppressing NF-kβ and MAPK pathways. *Tripterygium wilfordii* Hook F (TWHF) is used to treat glomerular nephritis, and *Radix puerariae*, also called kudzu, is used to treat diabetic nephropathy [92]. *Lespedeza capitata* (round-headed lespedeza) is a well-known ACE inhibitor. *Salvia milthiorrhiza* (Chinese sage, danshen) is used in USA and some Asian countries for blood

purification and rejuvenation of kidney cells. Some herbs like *Urticadioica*, *Nigella sativa*, *Silybum marianum* (milk thistle), *Parietaria judaica* (pellitory-of-the-wall, pellitory), and *Rheum palmatum* are all known for their nephroprotective properties [93]. In India, Cranberry or Vaccinium macrocarpon has been used for centuries to treat urinary tract infections (UTI) [94]. *Tribulus terrestris* and *Achyranthe saspera* are prescribed by ayurvedic practitioners as reducing agents for reducing the progression of renal tissue damage [95]. Equisetum arvense is known for its strong diuretic activity. Ocimum sanctum eliminates unwanted microbes and helps restore the microbial balance not only in the urinary tract but also in the whole body. It is also known for its anti-inflammatory activity, which reduces the stress in the tissues of the urinary system [96].

Drugs or therapeutic agents which decrease sodium content in the blood (edema) are termed diuretics. Edema is caused by a decrease in GFR, which is a probable outcome of kidney failure. Many chemically synthesized compounds or drugs are used as diuretics [97]. They have also been reported for their potential side effects. It has been assumed that nephrolithiasis and hyper-uricemia become complicated due to the treatment of certain diuretic agents. These enable the kidney to get excess water out of the body [98]. The nephroprotectivity of a compound protects kidney cells and their function against harmful substances. Certain plants produce nephroprotective phytoconstituents that help maintain the organ and prevent damage. These compounds also boost the performance of the kidney and provide cleansing activity. The aging of kidney cells can also be prevented, and healthier kidneys can be maintained for a longer time [99].

The property of a plant to cure a diseased state of the kidney is generally termed nephrocurative. They tend to repair the damaged cells in the kidney and help rejuvenate the kidney cells to increase their performance [100].

5. Ginger – A simple and effective solution for CKD

Zingiber officinale, commonly known as ginger, belongs to the Zingiberaceae family [101]. It is a spice used worldwide for its flavor and medicinal uses. Ginger is a widely used herb in many traditional medical practices like Chinese, Ayurvedic, Siddha, Unani, African, Caribbean, Tibetian, and Arabic. It is mainly found in tropical regions like India, China, Nepal, Nigeria, etc. Especially in India, it is cultivated almost in all states. This plant grows about 1 meter tall with long green and tapering leaves. The rhizome or the root of the plant is edible [102]. Traditionally it is used to treat cold, fever, head ache, tooth ache, asthma, rheumatism, sprains, sour throat, indigestion, constipation, hypertension, dementia, gastritis, loss of appetite, gingivitis, ulcer, infectious diseases, pregnancy-induced nausea, vomiting, muscle pain, back pain, abdominal pain, arthritis, hepatomegaly and sinusitis [103]. The phytochemicals present in ginger are essential oils, phenolic compounds, alkaloids, glycosides, flavonoids, terpenoids, saponin, tannin, protein, and carbohydrates [104].

Ginger possesses essential therapeutic activities like anti-hypertensive, anti-diabetic, anti-inflammatory, antioxidant, and nephroprotective. The compounds act against the respective root causes of the CKD like hypertension, diabetes, microbial infections, inflammation, reactive oxygen species, and drug toxicity (Figure 4).

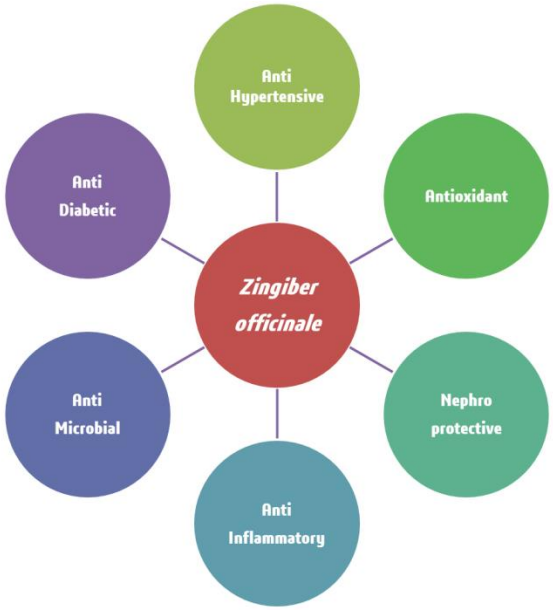


Figure 4. Therapeutic properties reported in *Zingiber officinale* related to CKD.

We performed an in silico docking study on selected phytochemicals from *Zingiber officinale* against a Chronic Kidney disease target. There are 64 phytochemicals identified and reported so far from *Zingiber officinale* [105], and these compounds were used for this docking process. All the 64 ligands were obtained from IMPPAT database and [106] Chemspider database [107], which are listed in Table 1.

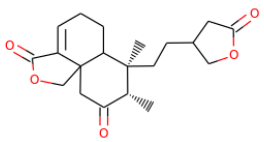
Table 1. List of phytochemicals identified from Zingiber officinale using IMPPAT and Chemspider databases.

S. No	Phytochemical identifier	Phytochemical name
1	CASID: 35949-86-1	[(2R,4R,5S,6R)-3,3,4,5-tetrahydroxy-2-propoxy-6-[[(2S,3S,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxymethyl]oxan-4-yl] (Z)-octadec-9-enoate
2	CID:101254152	Angelicoidenol
3	CID: 6428435	cis-Sesquisabinene hydrate
4	CID: 440966	(-)-camphene
5	CID:443158	(-)-Linalool
6	CID:10954686	10-Epizonarene
7	CID:443160	(+)-alpha-phellandrene
8	CID:10887971	(+)-Sabinene
9	CID:10407	(E)-beta-Farnesene
10	CID:12315493	(S)-3alpha-[(S)-1,5-Dimethyl-4-hexenyl]-6-methylenecyclohexene
11	CID:5318274	[4]-Gingerdiacetate
12	CID:5317587	[6]-Gingerdiol 3,5-diacetate
13	CHEMSPIDER: 4476884	1-(4-Hydroxy-3-methoxyphenyl)-3,5-octanediol
14	CID:5317590	1-(4-hydroxy-3-methoxyphenyl)tetradecane-3,5-diol
15	CID:9796015	1-Dehydro-6-gingerdione
16	CID:8914	1-Nonanol
17	CID:11552	3-Methylbutanal
18	CID:15839040	6-Gingerdiol
19	CID: 126890	6-Gingesulfonic acid
20	CID:5281794	6-Shogaol
21	CID: 5281516	Alpha-Farnesene
22	CID: 17100	Alpha-Terpineol
23	CID:10104370	Beta-Bisabolene
24	CID:11142	Beta-Phellandrene
25	CID:14896	Beta-Pinene
26	CID:12315492	Beta-Sesquiphellandrene
27	CID:638011	Citral
28	CID:22608831	Dehydro-10-gingerdione
29	CID:5354238	Dehydrozingerone
30	CID:22311	Dipentene
31	CID:339816	Diterpene II (Lactone)

S. No	Phytochemical identifier	Phytochemical name
32	CID:232	DL-Arginine
33	CID:424	DL-Aspartic acid
34	CID:1182	DL-Valine
35	CID:11127403	ent-Zingiberene
36	CID:2758	Eucalyptol
37	CID:7461	Gamma-Terpinene
38	CID:637566	Geraniol
39	CID:1549026	Geranyl acetate
40	CID:11369949	Gingerdiol
41	CID:162952	Gingerdione
42	CID:5281775	Gingerenone A
43	CID:5317592	Gingerenone B
44	CID:5317593	Gingerenone C
45	CID:10349562	Gingerglycolipid A
46	CID:10009754	Gingerglycolipid B
47	CID:3473	Gingerol
48	CID:750	Glycine
49	CID:8900	Heptane
50	CID:5318039	Hexahydrocurcumin
51	CID:5318568	Isogingerenone B
52	CID:442360	l-alpha-Curcumene
53	CID:5862	L-cysteine
54	CID:6306	l-isoleucine
55	CID:6106	L-leucine
56	CID:5951	L-serine
57	CID:6288	L-threonine
58	CID:10049	L(-)-Borneol
59	CID:86196543	Methyl-[12]-Gingediol
60	CID:31253	Myrcene
61	CID:643820	Nerol
62	CID:356	Octane
63	CID:25147318	Sesquithujene
64	CID:31211	Vanillylacetone

The obtained ligands were prepared as a single .pdb file. Further optimization and minimization of all ligands were done in PyRx software [108]. We have selected the Vitamin D3 receptor (VDR) (PDB ID: 1db1) [109] from the Therapeutic target database (TTD) [110], which is reported as a key target for therapeutics and diagnosis in CKD [111]. The 3D structure of the nuclear receptor for vitamin D complexed to vitamin D (PDB ID: 1db1) was downloaded from Protein Data Bank [112]. The target protein was downloaded in PDB format, and protein preparation was carried out in Swiss PDB Viewer [113]. The active site for the retrieved target protein was predicted using the PrankWeb server. The binding pocket with a high score and probability was chosen, and details of the Prankweb results are given in Table S1.

Table 2. Details of top, the binding score obtained phytochemical from *Zingiber officinale* against Vitamin D3 Receptor target protein (1db1).

No	Compound ID	Chemical name	2D structure	Score(Kcal/mol)
1	CID:339816	DITERPENE II (LACTONE)		-10.6

The phytochemical ligands were docked with nuclear receptors for vitamin D complexed to vitamin D (PDB ID: 1db1) using PyRx Docking software with default settings. Best docking complexes were generated and visualized in Biovia Discovery Studio Visualizer v21.1.0.20298. The docking results of all ligands with their binding score are shown in Table

S2. The best score generating phytoconstituent in the largest cluster was analyzed for its interaction with the protein, and its 2D and 3D structures were obtained from Biovia Discovery Studio Visualizer v21.1.0.20298. Out of 64 ligands used for docking, many ligands showed good binding scores. The top score was obtained by Ditepene (Lactone), the details of which are given in Table 2.

The 2D and 3D images of the best score generating phytoconstituent with the target are given in below in Figure 5.

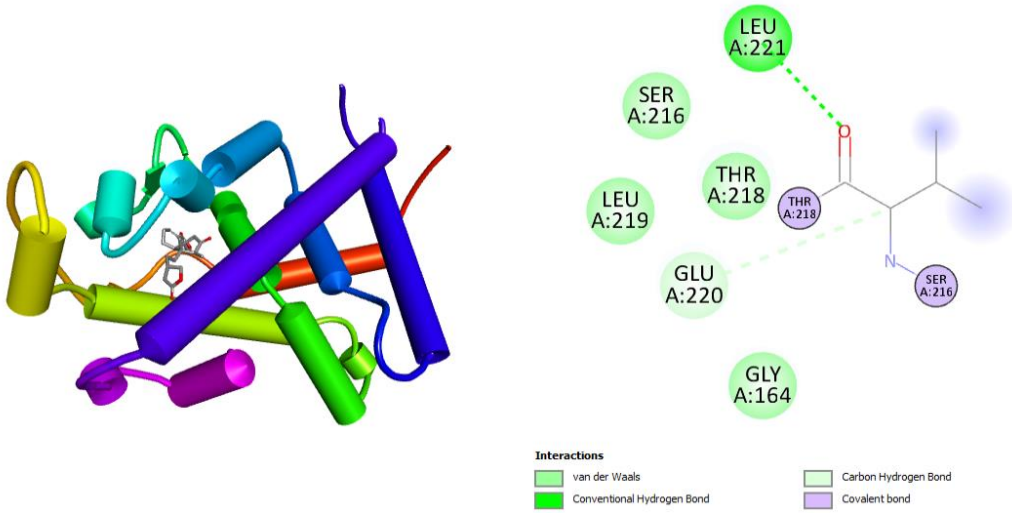


Figure 5. The 3D and 2D images represent the interaction of Diterpene (Lactone) with Vitamin D3 Receptor (VDR).

The pharmacokinetic properties and drug likeness were performed using the Swiss ADME server, which is given in Table 3.

Table 3. The list of pharmacokinetics properties includes physicochemical properties, lipophilicity, water-solubility, drug-likeness, and medicinal chemistry of selected compound Diterpene (Lactone).

Properties		CID:339816 DITERPENE II (LACTONE)
Physicochemical properties	Molecular Weight (g/mol)	346.42
	Heavy atoms	25
	Arom. heavy atoms	0
	Rotatable bonds	3
	H-bond acceptors	5
	H-bond donors	0
Lipophilicity	Log Po/w	2.30
Water solubility	Log S (ESOL)	Moderate
Pharmacokinetics	GI absorption	High
Drug likeness	Lipinski rule	Yes; 0 violation
Medicinal Chemistry	Synthetic accessibility	Easy

Table 4. List of the drug-induced hERG inhibition, AMES toxicity, carcinogens, Tetrahymena pyriformis (TP) toxicity, honeybee (HB) toxicity, acute rat toxicity (LD50 in mol/kg) along with P-glycoprotein inhibitor (PGI) activity of selected compound Diterpene (Lactone).

Compound ID	**heRG inhibition**	**AMES**	**Carcinogens**	***T.Pyriformis* toxicity (log ug/L)**	**Hepato toxicity**	**PGI**	**Oral Rat Acute Toxicity (LD50) (mol/kg)**	**Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)**
CID:339816 DITERPENE II (LACTONE)	No	No	No	0.504	No	Inhibitor	2.046	1.734

The toxicity prediction of the top hit molecule Diterpene (Lactone) was predicted using the pkCSM server, and the results of which are given in Table 4.

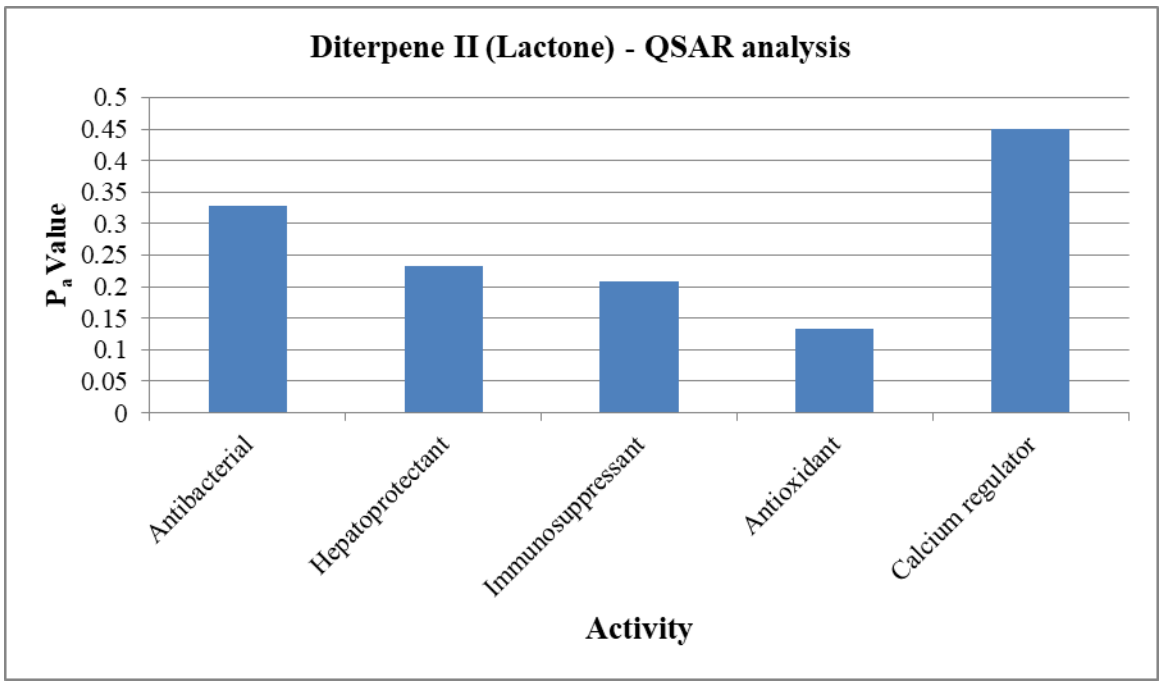


Figure 6. The PASS server output of the Diterpene II (Lactone); Y-axis represents the Pa (probability) value, while X-axis represents the bioactivity.

To validate the suitability of lead compound, QSAR analysis was performed using the PASS Server [114]. The key bioactivities of diterpene II (Lactone) associated with CKD were reported, with its Pa value ranging between 0.1 – 0.45, which is represented in Figure 6. Bacterial infection, inflammatory responses, and free radicals are some of the leading causes of CKD, which are addressed by properties like antibacterial, immunosuppressant, and antioxidant. Renal failure is one of the severe complications associated with patients with liver cirrhosis [115]. Thus, the hepatoprotective property of the compound aids in CKD prevention. The kidney plays a major role in calcium homeostasis [116] and gets targeted by the calcium regulators. Thus, the calcium regulators' role of compounds can contribute to calcium homeostasis.

Biotransformation of a molecule plays a crucial role in the process of drug development and optimization. Diterpene displays a wide range of biological activities, making this a promising compound for biotransformations [117]. Patents using biotransformation approaches are available for diterpene to prepare anticancer, antiproliferative, and immunosuppressive agents, highlighting the importance of diterpenes biotransformation in the health industry.

Ginger has also been reported for the following medicinal properties: antifungal, anti-diarrhea, immune-modulatory, antiemetic, anti-lipidimic, anti-apoptotic, and anti-tumorogenic anti-arthritic, anti-neoplastic, analgesic, cytotoxic and hepatoprotective activities [118]. One of the major constituents of ginger is gingerol. Gingerol, upon thermal processing, degrades into shogaols, which have greater thermal and acidic stability [119].

Ginger is being extensively studied for various pharmacological activities, but its nephroprotective property is comparatively less explored. Ethanolic extracts of ginger showed better reno-protective activity at a concentration of 250 mg/kg in combination with a-tocopherol in cisplatin-induced nephrotoxic rats [118]. Aqueous extracts of ginger lowered

blood glucose, serum urea, and creatinine levels in diabetic-induced rats. It also helped to restore the changes in the kidney caused due to toxicity. This results in normalized blood glucose level, glutathione peroxidase (GPX) activity increase, and serum lipid peroxidase level [120]. Ginger is known for its antioxidant activity as well. In a study involving cadmium-induced renal toxicity, ethanolic extracts of ginger increase the body and kidney weight and prevent cadmium accumulation in the kidney. The ginger extract improved renal function, increased creatinine clearance, and reabsorption of glomerular-filter albumin. The urea content in the blood is also significantly low, and it was said to prevent renal tissue and DNA damage [121]. Oral treatment with ethanolic extracts of ginger in STZ-induced diabetic rats showed changes in glomeruli and renal tubules. It also protects renal tissues from structural damage caused by hypoglycemia, inhibits cholesterol absorption due to oxidative stress, and also boosts the kidney's defense mechanism. It decreases protein carbonyl and malondialdehyde (MDA), a lipid peroxidation marker [122]. Ginger juice and metformin we used to treat gentamycin-induced nephrotoxic rats showed an excellent reno-protective activity. Its combination was found to be more effective than individual aliquots, and it is considered a better option to treat diabetic nephropathy [123].

Ginger extracts increase superoxide discriptase, antioxidant enzymes, CAT levels and reduce MDA in metalaxyl-induced kidney damage. Ginger extracts ameliorate kidney functions and lower nitrosapive stress and lipid peroxidation levels [124]. It also discovered that the prolonged treatment with ethanolic extracts of ginger brought cytoplasm and mitochondrial enzymes like glucose-6-phosphate-dehydrogenase (G6PD), Lactate dehydrogenase (LDH), Glutamate dehydrogenase (GDH), Malate dehydrogenase (MDH), and Formate dehydrogenase (FDH) levels are back to normal in streptozotocin-induced rats [125]. It showed an increase in body weight increase in the secretion of insulin from β cells of the pancreas, and it reversed the renal tissue damage. The increase in G6PD levels after treatment may be due to the antioxidant property of shogoals, gingerol, and zingeberone [126]. The animals receiving ginger extracts showed a reduction in blood urea nitrogen due to inhibition of urea reabsorption in the nephrons. Ginger extracts are also effective in removing urea from plasma and showed little effect on the excretion of creatinine in the urine [127]. It was established that the presence of polyphenols and flavonoids account for the antioxidant and nephroprotective activity of ginger [128]. Ginger inhibits the production of various cytokines, including IL-1, IL-8, and TNF-α. Gingerol and gingerdione inhibit PGE-2 synthesis; 10 gingerol, 10 shogoal, and 8 shogoals inhibit COX-1, 2, and 5-lipooxygenase, which overall results in the suppression of leukotriene and exhibits nephroprotective effects [129]. Ethanolic extracts of ginger and vitamin E (a- tocopherol) showed nephroprotective activity triggered either by the direct antioxidant activity of ginger or by preventing the decrease in renal antioxidant activity in cisplatin-induced nephrotoxic rats [130].

6. Ginger Compress Therapy for Renal Failure Patients

Massage is defined as a scientific influence of soft tissue in the body with rhythmic pressure and stroking, providing pain relief through several mechanisms and promoting physical and mental relaxation [131]. Massage therapy or compress therapy was first practiced in China in the second century BC, and soon migrated to India in 400 BC [132]. It was defined as "the art of rubbing" [133]. It is considered a part of alternative medicine. Compress therapy uses hands to manipulate the soft tissues to bring the desired change in the individual [134]. The fundamental massage/compress techniques involve touch, vibration, compression,

stroking, rubbing, kneading, and percussion [135]. Compress therapy usually involves the power of touch and the property of aromatic oils. These oils are effectively absorbed by the skin into the bloodstream through massage in a shorter period of time. The stroking and kneading relax the muscles and soft tissues [136]. Sufficient pressure must be applied to the specific trigger points to achieve the desirable effects. Trigger points are small contracting knots in the skeletal muscle associated with triggering the subcutaneous tissue to produce the desired effect [137]. The benefits of compress therapy include improved circulation, relaxes muscles, trigger the healing process, removes waste metabolites, reliefs pain, increased spirit, promotes balance in the body, increased nutrition availability to the tissue, and releases endorphins from the brain, which promotes relaxation, and pain relief [138].

Ginger compress therapy has been developed for kidney failure and diabetic patients. Ginger has accounted for various medicinal uses from ancient times. But most of them lack proper documentation and scientific validation. This therapy was identified in the book "ayurveda: secrets of healing" by Maya Tiwari [139]. It has been assumed to cure kidney failure followed by termination of dialysis. Many local ayurvedic and Siddha practitioners have followed this procedure and claimed that it is working on their CKD patients. The procedure of ginger massage is given in the book as follows:

6.1. Ginger massage procedure.

Washed ginger of about 125 grams is taken, washed, and cut into pieces. The ginger pieces were crushed and taken in a white cloth and tied. Three liters of water are taken and allowed to boil. Once it boils and bubbles occur, the tied ginger cloth is put into the boiling water. The vessel is closed with a plate, and the flame is lowered for 20 to 30 minutes. After 30 minutes, the flame is put off, and the vessel is kept aside for 5 to 10 minutes. After that, the vessel is taken near the patient, and the patient is asked to lie down on the stomach. Take a towel, soak it in the ginger water, partially press it, and spread the towel over the lower portion of the patient's back. Do it at least 7 to 8 times for 30 minutes. After massaging, rub the lower portion with 4 to 5 drops of gingili oil. The same procedure is depicted in Figure 7.

Figure 7. The pictorial depiction of the ginger compress therapy procedure.

It has been advised to check the urea, creatinine, odor, and urine volume. It has been assumed that following ginger therapy, there will be an increase in urine output and would make the patient more energetic.

7. Conclusions

The CKD is a chronic disorder that puts the patients physically and mentally suffer. An effective permanent cure for this is not available to date. The existing treatment option doesn't focus on treating the root cause of the disease; instead, it adds more financial and mental burdens to the patients. Hence, there is a need for alternative medicine or therapy, for which 'Ginger Compress Therapy' could be a better option. The nephrocurative and nephroprotective properties of ginger which many researchers have reported, make it a promising alternative to the existing treatment methods. Also, the authors' in silico molecular docking studies indicated the presence of potentially bioactive compounds in ginger, which has shown better binding efficiency against the target of CKD. This study focused only on *in silico* analysis based on which diterpene (Lactone) has shown high binding efficiency with the Vitamin D3 Receptor, the target protein, but further exploration needs to be carried out using *in vitro* and *in vivo* methods. Since this therapy is a home-based treatment and low cost, it is advantageous to the patients. Thus, extensive research focusing on this 'Ginger Compress Therapy' is the need of the time which can bring more knowledge on its efficacy and viability.

Funding

No financial support.

Acknowledgments

The authors acknowledge Kalasalingam Academy of Research and Education, Krishnankoil, India.

Conflicts of Interest

The authors declare no competing financial interest and no conflicts of interest.

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Supplementary material

Table S1. Active Site Prediction using Prankweb Server.

Name	Rank	Score	Probability	Sas_points	Surf_atoms	Center_x	Center_y	Center_z	Residue_ids	Surf_atom_ids
pocket1	1	52.41	0.948	112	63	10.5575	23.1141	34.1817	A_142 A_143 A_144 A_147 A_150 A_227 A_230 A_231 A_233 A_234 A_236 A_237 A_240 A_268 A_271 A_272 A_274 A_275 A_278 A_286 A_288 A_295 A_300 A_305 A_309 A_313 A_397 A_401 A_404 A_414 A_418 A_422	187 192 200 201 203 206 232 234 259 261 454 475 477 479 480 481 482 500 501 507 508 522 524 528 532 555 771 794 801 817 820 824 827 828 851 912 913 914 915 916 917 918 919 920 934 989 990 991 1034 1035 1068 1070 1101 1132 1782 1784 1815 1817 1845 1924 1952 1984 1986
pocket2	2	1.45	0.008	34	22	15.6935	22.9369	56.8706	A_269 A_336 A_340 A_342 A_356 A_360 A_380 A_384 A_387 A_388 A_391	779 1321 1349 1363 1364 1465 1466 1467 1499 1500 1645 1672 1675 1676 1697 1698 1699 1701 1703 1704 1731 1732
pocket3	3	0.88	0.002	7	12	14.5379	13.4841	42.9678	A_139 A_142 A_240 A_241 A_244 A_274 A_334	162 189 552 553 559 560 582 583 819 820 1308 1309

Table S2. The binding affinity of ligands from Zingiber officinale against Vitamin D3 Receptor (1db1) protein.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
1db1_1_Target_Preprocessed_DITERPENE_II_(LACTONE)_uff_E=765.88	-10.6	0	0
1db1_1_Target_Preprocessed_Gingerenone_B_uff_E=327.58	-9	0	0
1db1_1_Target_Preprocessed_Gingerenone_C_uff_E=215.21	-9	0	0
1db1_1_Target_Preprocessed_Gingerenone_A_uff_E=286.70	-8.8	0	0
1db1_1_Target_Preprocessed_Isogingerenone_B_uff_E=366.43	-8.8	0	0
1db1_1_Target_Preprocessed_Gingerdione_uff_E=143.55	-8.6	0	0
1db1_1_Target_Preprocessed_1-Dehydro-6-gingerdione_uff_E=221.12	-8.6	0	0
1db1_1_Target_Preprocessed_6-Gingesulfonic_acid_uff_E=587.65	-8.5	0	0
1db1_1_Target_Preprocessed_l-alpha-Curcumene_uff_E=124.37	-8.5	0	0
1db1_1_Target_Preprocessed_6-Gingerdiol_uff_E=173.36	-8.4	0	0
1db1_1_Target_Preprocessed_ent-Zingiberene_uff_E=191.39	-8.4	0	0
1db1_1_Target_Preprocessed_Gingerdiol_uff_E=239.97	-8.4	0	0
1db1_1_Target_Preprocessed_gingerol_uff_E=235.45	-8.4	0	0
1db1_1_Target_Preprocessed_6-Shogaol_uff_E=130.09	-8.3	0	0
1db1_1_Target_Preprocessed_Dimethyl-4-hexenyl]-6-methylenecyclohexene_uff_E=177.10	-8.3	0	0
1db1_1_Target_Preprocessed_Gingerglycolipid_B_uff_E=574.01	-8.3	0	0
1db1_1_Target_Preprocessed_Hexahydrocurcumin_uff_E=235.90	-8.2	0	0
1db1_1_Target_Preprocessed_alpha-Farnesene_uff_E=149.16	-8.1	0	0
1db1_1_Target_Preprocessed_Gingerdiacetate_uff_E=186.13	-8.1	0	0
1db1_1_Target_Preprocessed_1-(4-Hydroxy-3-methoxyphenyl)-3, 5-octanediol_uff_E=197.74	-8.1	0	0
1db1_1_Target_Preprocessed_beta_uff_E=135.13	-8	0	0
1db1_1_Target_Preprocessed_cis-Sesquisabinene_hydrate_uff_E=1529.25	-7.9	0	0
1db1_1_Target_Preprocessed_Gingerglycolipid_A_uff_E=583.46	-7.9	0	0
1db1_1_Target_Preprocessed_Epizonarene_uff_E=215.78	-7.8	0	0
1db1_1_Target_Preprocessed_octadec-9-enoate_uff_E=900.89	-7.8	0	0
1db1_1_Target_Preprocessed_sesquithujene_uff_E=1426.98	-7.8	0	0
1db1_1_Target_Preprocessed_1-(4-hydroxy-3-methoxyphenyl)tetradecane-3, 5-diol_uff_E=196.40	-7.7	0	0
1db1_1_Target_Preprocessed_Dehydro-10-gingerdione_uff_E=338.24	-7.6	0	0
1db1_1_Target_Preprocessed_Gingerdiol_3, 5-diacetate_uff_E=327.40	-7.6	0	0
1db1_1_Target_Preprocessed_Methyl-[12]-Gingediol_uff_E=311.55	-7.5	0	0
1db1_1_Target_Preprocessed_beta-Bisabolene_uff_E=195.03	-7.3	0	0
1db1_1_Target_Preprocessed_Dehydrozingerone_uff_E=193.44	-7.3	0	0
1db1_1_Target_Preprocessed_beta-Sesquiphellandrene_uff_E=199.53	-7.2	0	0
1db1_1_Target_Preprocessed_GERANYL_ACETATE_uff_E=114.66	-7.2	0	0
1db1_1_Target_Preprocessed_Vanillylacetone_uff_E=113.96	-7.1	0	0
1db1_1_Target_Preprocessed_Dipentene_uff_E=133.30	-6.7	0	0
1db1_1_Target_Preprocessed_alpha-TERPINEOL_uff_E=149.41	-6.6	0	0
1db1_1_Target_Preprocessed_GAMMA-TERPINENE_uff_E=66.93	-6.6	0	0
1db1_1_Target_Preprocessed_GERANIOL_uff_E=117.27	-6.6	0	0
1db1_1_Target_Preprocessed_alpha-phellandrene_uff_E=157.54	-6.5	0	0
1db1_1_Target_Preprocessed_BETA-PHELLANDRENE_uff_E=129.56	-6.5	0	0
1db1_1_Target_Preprocessed_Citral_uff_E=100.70	-6.5	0	0
1db1_1_Target_Preprocessed_BETA-PINENE_uff_E=710.26	-6.2	0	0
1db1_1_Target_Preprocessed_MYRCENE_uff_E=99.32	-6.2	0	0
1db1_1_Target_Preprocessed_Sabinene_uff_E=1429.66	-6.2	0	0
1db1_1_Target_Preprocessed_Angelicoidenol_uff_E=495.25	-6.1	0	0
1db1_1_Target_Preprocessed_DL-Arginine_uff_E=164.59	-6.1	0	0
1db1_1_Target_Preprocessed_Eucalyptol_uff_E=344.71	-6.1	0	0
1db1_1_Target_Preprocessed_Linalool_uff_E=97.84	-6.1	0	0
1db1_1_Target_Preprocessed_camphene_uff_E=355.27	-6	0	0
1db1_1_Target_Preprocessed_nerol_uff_E=118.32	-6	0	0
1db1_1_Target_Preprocessed_1-Nonanol_uff_E=47.34	-5.7	0	0
1db1_1_Target_Preprocessed_L-leucine_uff_E=151.93	-5.6	0	0
1db1_1_Target_Preprocessed_l-isoleucine_uff_E=166.76	-5.5	0	0
1db1_1_Target_Preprocessed_DL-ASPARTIC_ACID_uff_E=144.81	-5.4	0	0

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
1db1_1_Target_Preprocessed_octane_uff_E=23.02	-5.1	0	0
1db1_1_Target_Preprocessed_DL-Valine_uff_E=152.37	-5	0	0
1db1_1_Target_Preprocessed_L-threonine_uff_E=153.53	-4.8	0	0
1db1_1_Target_Preprocessed_HEPTANE_uff_E=20.11	-4.7	0	0
1db1_1_Target_Preprocessed_L-serine_uff_E=155.95	-4.7	0	0
1db1_1_Target_Preprocessed_3-Methylbutanal_uff_E=20.61	-4.4	0	0
1db1_1_Target_Preprocessed_L-cysteine_uff_E=150.10	-4.2	0	0
1db1_1_Target_Preprocessed_glycine_uff_E=113.04	-3.8	0	0
1db1_1_Target_Preprocessed_L(-)-Borneol_uff_E=91.45	-1.1	0	0