INNOVATIONS

Natural Flavanones – A Target in The Treatment of ADPKD

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Abstract:

Autosomal dominant polycystic kidney disease [ADPKD] is a genetic disorder in a very dominant pattern, where it shows number of cysts in urinary system. Symptoms may vary in severity; sometimes symptoms develop in late 30's. These symptoms get worse with time and age. ADPKD is most frequently caused by changes within the Polycystic Kidney Disease [PKD_1 and PKD_2]genes and fewer typically by changes within the *GANAB* and *DNAJB11* genes. In recent years, attention has been focused on the use of natural sources of antioxidants in the prevention of chronic diseases. Flavanones are the examples of such substances. Flavanones-rich products include citrus fruits, grapes, cherries, parsley, oregano, etc. Flavanones exhibit a wide range of uses, such as prevention of chronic diseases, including metabolic disorders, renal disorders, diabetes, cardiovascular disease, etc. because of their beneficial effect on blood lipids, blood pressure, plasma glucose levels, stabilization of athetosclerotic plaque, some types of cancer, Alzheimer's disease, Parkinson's disease, some viral infections, cataract, erectile dysfunction and inflammatory bowel disease. Consumption of Flavanones with diet appears to be safe. There is a growing body of evidence that a diet rich in these substances is beneficial for health and its promotion is thus justifiable.

Keywords: 1. Autosomal dominant polycystic kidney disease [ADPKD] 2.Genetic disorder 3. PKD genes 4. Flavanones.

Introduction:

Autosomal dominant polycystic kidney disease [ADPKD] is a genetic disorder in a very dominant pattern, where it shows number of cysts in urinary system. Symptoms may vary in severity; sometimes symptoms develop in late 30's. These symptoms get worse with time and age. ADPKD is most frequently caused by changes within the PKD_1 and PKD_2 genes, and fewer typically by changes within the *GANAB* and *DNAJB11* genes.[1]. Treatment for ADPKD involves symptom management and reducing progression of disease. [2]Conventional treatment for ADPKD symptoms include – Antihypertensives, Antibiotics to treat infections in kidney or liver cysts or UTI, Analgesics.

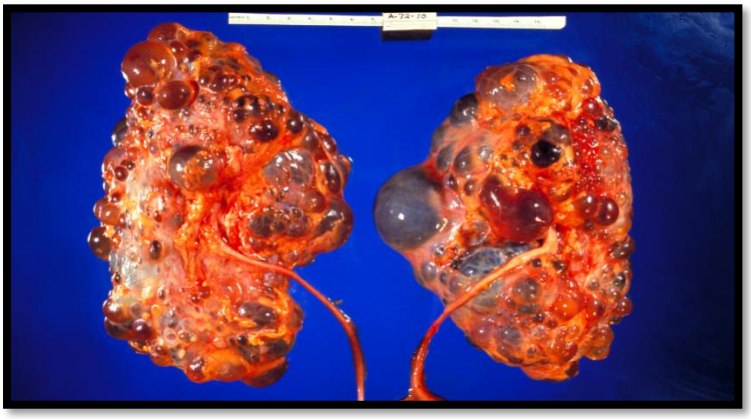

Fig. No. 1: Polycystic kidneys

Symptoms:

ADPKD affected people may face the following complications:[3]

- Algesia in kidney region and headache.
- Hypertension
- UTI's, kidney and liver infections.
- Hematuria
- Kidney, Liver and pancreatic cysts
- Kidney stones
- Brain aneurysm

Some people with ADPKD have few or no symptoms and may be diagnosed by accident or chance [1][4]. Eventually the formation of multiple kidney cysts leads to kidney damage and kidney failure[3][4].

Statistics:

The exact number of people with ADPKD is unknown. ADPKD may affect 1 in 500 people. The most common form of inherited kidney disease is ADPKD [1].

Etiology:

ADPKD is caused by genetic changes in the PKD1, PKD2, GANAB and DNAJB11 genes. [3][4]. It can transmit as Autosomal dominant trait. With sudden mutations of the genes, ADPKD can affect without any family history also. [3]

Pathophysiology:

The disease is characterized by slow development of large fluid filled cysts which enlarge the kidneys and compromise the functional integrity of nephrons. 50% of ADPKD patients will progress to

end stage renal disease, requiring transplant or dialysis [5], [6], [7]. Heterogeneity of the disease can be explained by somatic mutations. Modifier genes may also be inherited independently of the PKD mutation and increase the disease severity. Examples of modifier genes are CFTR gene, angiotensin-1-converting enzyme [ACE] gene [8], [9], [10], [11], [12], [13].

85–90% of ADPKD patient cases are due to mutations in PKD1 gene, while another 10–15% of cases are due to mutations in PKD2 [14]. Patients with mutations in PKD1 may experience more severe symptoms than PKD2 gene mutations. At present, 300 mutations of PKD1 and 91 mutations of PKD2 have been identified in patients with ADPKD.

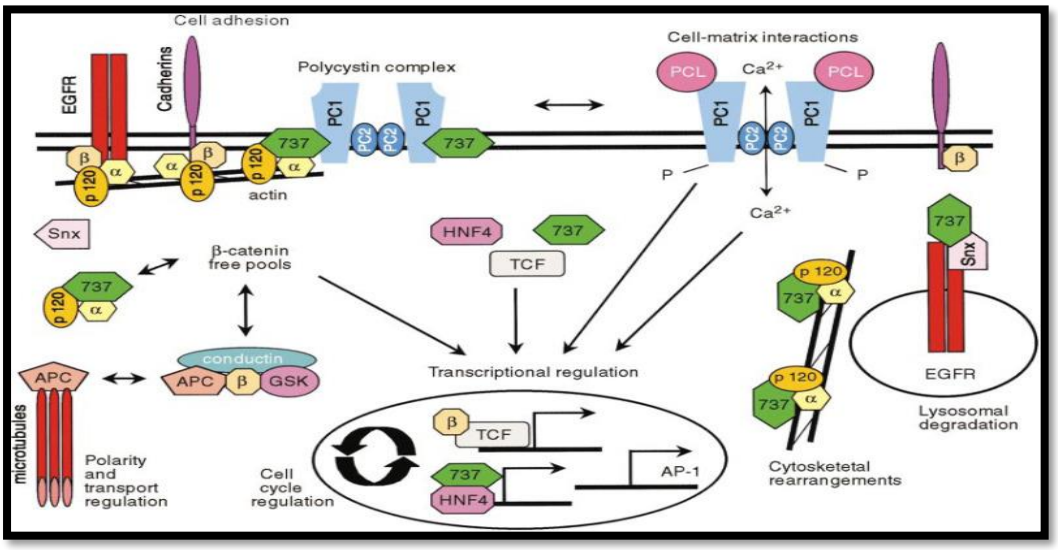

Fig. No. 2: Intracellular signaling pathways

Genetics of ADPKD:

ADPKD is hereditary and can cause by mutations in genes - PKD1 and PKD2 [15,16]. Mutations in chromosome 16p13.3 of PKD1 located is the reason for 85% of cases, whereas mutations in chromosome 4q21–23 of PKD2 are reason for 15% of cases. [17,18]. Mutations of these genes can cause changes in cytoskeleton and morphological changes in real system. Compared with PKD1 patients, PKD2 patients have longer renal survival rate and have less complications [19].

The PKD1 gene consists of 46 exons, is very large, observed over 52 kb of genomic DNA [20, 21]. The gene encodes a 14.1-kb mRNA transcript, where translation occurs to form a protein comprises of 4302 amino acids. Mutations in PKD1 gene can be found all over the gene. Recently, by the help of denaturing HPLC [DHPLC], long-range PCR and the protein truncation test, mutations which occur all over the PKD1 gene have been identified [22,23,24]. The PKD2 gene encodes a 5.3-kb mRNA transcript and is present on chromosome 4q21–23, which is translated into protein containing 968 amino acid. Same as in PKD1, mutations have been found all over the gene [25]. Some of the mutations identified are frameshift, splicing, or nonsense mutations. PKD2 gene is not duplicated like PKD1 [26].

Polycystin-1

The proteins which PKD1 and PKD2 genes encode are the polycystins[PC's]. They play an important role in fertilization, ion translocation, and mechanosensation. PKD1 gene encodes Polycystin-1, which has 4302 amino acids and molecular weight is 500,000 D [21,27,28]. As shown in Figure 1, PC-1 is an integral membrane protein, which has 11 transmembrane segments and 16 immunoglobin-like domains called PKD repeats. The large, extracellular amino-terminal domain contains two leucine-rich repeats coded by cysteine-rich domains, a C-type lectin domain, a WSC domain. Sea urchin egg jelly receptor [29] and proteolytic cleavage site [GPS domain] are present near the membrane [30,31]. A region of similarity to lipoxygenases [PLAT domain] is present between the first and second transmembrane [31,32]. The carboxyl-terminus of PC-1 is present in cytoplasm and contains a domain that regulates protein-protein interactions. Proteolytic cleavage at the GPS domain in PC-1 is important in mutations with polycystin function [64].

Polycystin-1 and polycystin-2 homologues in C. elegans are useful for stereotyped mating behavior caused by ciliated sensory neurons. Polycystin proteins in C. elegans, function as mechanosensors or chemosensors[34,35]. PC-1 gene regulates G protein signaling. The c-terminal of PC-1 bind to G proteins and activates $G\alpha i/o$ and releases $G\beta\gamma$ subunits [36,37]. Signaling though this pathway is antagonized by PC-2. G - Protein signaling pathways regulate cyst formation, fluid secretion, proliferation, cell polarity and differentiation [38,39]. The main feature of cystic epithelial cells is high rate of cellular proliferation [40,41,42]. Overexpression of PC-1 in MDCK cells to regulate cellular proliferation and reduce cyst formation [43]. Polycystin-1 can directly arrest the cell cycle at the G0/G1 transition [44].

Polycystin-2

Polycystin-2 protein is encoded by PKD2 gene, which has 968 amino acids [45]. Ipolycystin-2 is also an integral membrane protein. It has intracellular amino- and carboxyl-termini and 6 transmembrane segments. Polycystin-2 receptor has some similar structural features with, voltage-activated calcium channels, transient receptor potential [TRP] and sodium channels. It is mostly present in tissues of kidney, ovary, heart, vascular smooth muscle, small intestine and testis[46,47]. Polycystin-2 protein is expressed in all nephrons in kidney, except glomeruli. Polycystin-2 showsits actions through ion channel [48–51]. It inhibits G - protein signaling [52]. Most of polycystin-2 protein is present in Golgi complex and endoplasmic reticulum [ER]. Studies show that raise in ER markers are also one of the symptoms of ADPKD [53,54, 55].

Polycystin-2 increases calcium release from intracellular calcium reserves in stimulation with hormones which transiently increases cytosolic calcium [54]. Studies show that polycystin-2 rises cytosolic calcium, thus reduced capacity to translocate calcium, reduced kidney function, trigger exocytosis and changes in gene expression leading to polycystic kidney disease.

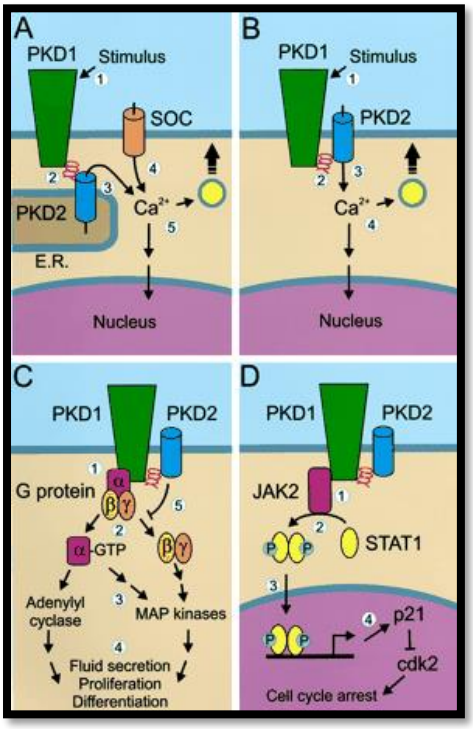

Fig. No. 3: Models of Polycystin-1/ Polycystin-2

Ciliopathies and renal cystic disease:

Primary cilium is the main area for many proteins involved in renal cystogenesis. Tg737 gene function was disrupted in the Oak Ridge Polycystic Kidney mouse [Tg737orpk] model [54], IFT88 mutant mice defects including cystic and enlarged kidneys [56].

GFP-tagged mammalian polycystin-1 and polycystin-2 were present in the ciliated tips of Caenorhabditis elegans male sensory neurons, as well as primary cilium in human and mouse kidney cell lines [55], [57], [58]. Ciliary polycystins play an important role in regulating cellular response, increase in intracellular calcium, thereby primary cilium act as a mechanosensor [49], [59], [60]. Polycystins also function with the JAK/STAT [61], [62], p53 [63], mTOR [64], NFAT/AP-1 [65] or Wnt signaling pathways [61], [66], [67]. If the polycystins are mutated, one of these cellular signaling alters and cystogenesis starts.

Mechanism of cyst growth — fluid secretion:

Cysts originate as dilatations in the walls of tubules, followed by filling glomerular fluid [68]. The cyst formation in ADPKD is idiopathic, but some of the scientists say that it is completely due to genetical mutations. [68,69,70]. These changes in cells of cilia and nephrons in response to mutations [69], [71], cause abnormal protein targeting [58, 72], cyclic AMP activation [68, 73, 74] and uncontrollable cell proliferation and growth [75, 76, 77, 78, 79].

The pathological processes are as follows: 1] increase in glomerular filterate fluid secretion into the cyst lumen and 2] uncontrollable increase in mitosis in cell division of the cyst lining. 3] This

increases the hydrostatic pressure inside the cyst and causes expansion, 4] This will simultaneously induce de novo cyst formation. The rate of fluid secretion into the cyst lumen is directly proportional to the amount of the CFTR chloride channel present in the apical membrane [80]. In vitro cyst fluid production by PKD cells is estimated to be range from 26 to 475 ml per year [81].

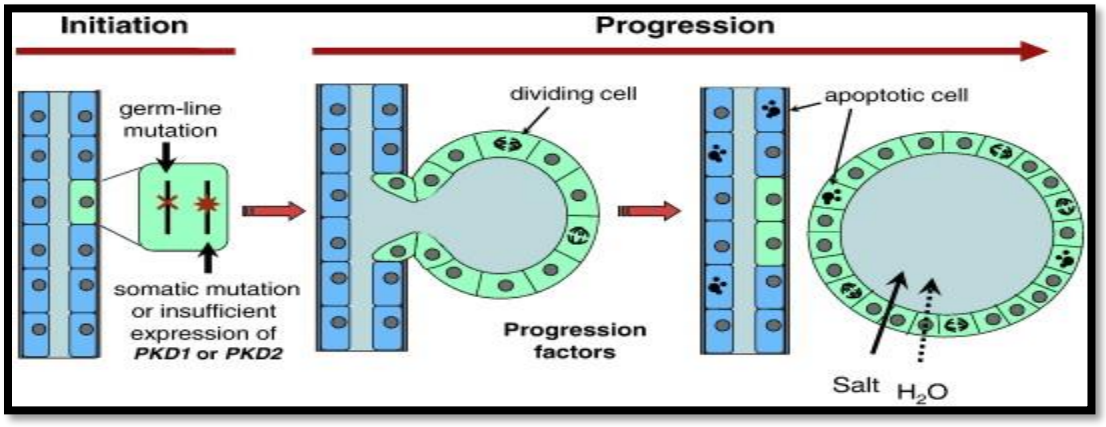

Fig. No. 4: Mechanism of cyst growth

The fluid secretion by renal cyst epithelia cells, is mediated by Na+K+-ATPase in the basolateral membrane, which release sodium extrusion and potassium uptake. Sodium again enters the cell via a basolateral isoform of the sodium–potassium chloride cotransporter [NKCC1], which cause basolateral chloride entry. This chloride moves out via CFTR channel, by the electrochemical gradient across the apical membrane. The chloride movement cause paracellular sodium and water movement, thus causing fluid accumulation within the cyst lumen [82].

In some patients with cystic fibrosis and PKD, the PKD progression is slower than Cystic fibrosis, because the mutated CFTR channel cant cause fluid secretion [121]. The CFTR chloride channel is activated by increase in cytosolic levels of cAMP [83]. cAMP cause mitogenic stimulus for cyst epithelial cells [84], [85].

Kidney Disease Stages:

Table 1: Stages of kidney disease

CKD stage	Kidney function	eGFR [estimated glomerular filtration rate]in ml/min/1.73 m2
1	Normal	90 or more
2	Mildly reduced	60 to 89
3	Moderately reduced	30 to 59
4	Severely reduced	15 to 29
5	Very severely reduced = kidney failure	Less than 15 [or having dialysis]

Diagnosis:

Diagnosis is done based on the clinical symptoms, hereditary and imaging studies of the kidneys.

Some of the diagnostic kidney imaging methods is as follows:

- Ultrasound
- Computerized Tomography [CT] scans or
- Magnetic Resonance imaging [MRI]. [86]
- Genetic testing - It is performed first in people who have the symptoms of ADPKD for mutated genes, the for the unaffected family members, to determine if they will develop the ADPKD or not. [87].

Treatment:

Treatment for ADPKD include management of both kidney and non-kidney symptoms. When kidney function decreases, treatment is targeted at slowing down the progression to kidney failure, by controlling hypertension and proper diet maintenance. In end stage renal failure, dialysis or kidney transplantation are the main options [88].

Some of the potential therapeutic targets focus on fluid secretion, while others on cellular growth and proliferation. Increase in cAMP levels is the common pathologyin ADPKD [89,90].. cAMP is also show stimulation of the MAPK/ERK signaling pathway via Src and Ras [91]. Vasopressin levels are increased in human ADPKD [92]. The upregulation of V2 receptor stimulates cAMP accumulation. V2 receptor blockers [clinical trials are going on Tolvaptan]showed a promising therapeutic target in cystic disease [93]. Activating the somatostatin receptor by their agonists reduces cellular cAMP levels [94]. Other targets are CFTR inhibitors and KCa3.1 inhibitors, which inhibit the basolateral potassium entry necessary for cAMP-dependent chloride secretion [95, 96].

Fda-Approved Treatments:

Tolvaptan is FDA-approved drug under brand name: Jynarque - Manufactured by Otsuka Pharmaceuticals Co., Ltd. in April 2018. Indication is to slowdown the cysts formation in people who are at risk of ADPKD [97].

Prevention [98]:

- Antihypertensive.
- Maintenance of proper diet containing low sodium.
- Maintaining of correct BMR
- Away from tobacco and alcohol
- Moderate physical activity.

Flavanones

Flavanones are also called as dihydroflavones. They have a saturated C ring and the double bond position between 2 and 3 carbons. During last 15 years the research on flavanones has been increasing [99]. Flavanones are usually present in all citrus family fruits like lemons, oranges and grapes. Some of the examples of this class of flavonoids are Hesperitin, naringenin and eriodictyol[Fig. 5]. Flavonones have a numerous pharmacological effects because of their Antioxidant / free radical-scavenging properties. They impart bitter taste for the juice and peel of citrus fruits. Other uses of such flavonones are anti-inflammatory, blood lipid-lowering and cholesterol-lowering agents.

Flavonone Mechanisms:

Body cells and tissues are frequently damaged by free radicals and reactive oxygen species, which are produced during normal oxygen metabolism or are induced by exogenous damage[100,101]. The mechanisms by which the free radicals damage the cellular functions are not completely known. But most of the cellular protection events target lipid peroxidation, which results in cellular damage. This damage causes net changes in the osmotic pressure, leading to inflammation swelling and eventually Apoptosis or necrosis. Many inflammatory mediators can be attracted by free radicals. This starts a new inflammatory response and tissue damage. Several protective mechanisms have adopted by the living things in order to protect from free radicals[102]. Some of the antioxidant defence mechanisms are enzymatic reactions like catalase, superoxide dismutase and glutathione peroxidase, but also non-enzymic reactions like ascorbic acid, glutathione and α-tocopherol. During the injury, there will be increase in production of free radicals and there will be decrease in the endogenous scavenging compounds. Flavonones have a synergistic effect to the endogenous scavenging compounds[103]. Codorniu-Hernández et al.[104] carried out docking studies on flavonone–protein interactions. Hydrophilic amino acid residues have high-affinity interactions with flavonone molecules. The docking modes among catechin molecules and four proteins [human serum albumin, transthyretin, elastase and renin] also prove the affinity information.

Dietary Sources of Flavanones:

- **Dietary Flavonoids [aglycones]** - Eriodictyol, Hesperetin, Naringenin, Iso Sakuratenin, Heridictyol
- **Common Food Sources** - Citrus fruit and juices, e.g., oranges, grapefruits, lemons

Table 2: Amount of Flavanones in natural sources

Food Sources	Naringenin	Hesperetin	Eriodictyol
Grapefruit juice, white, fresh	18.2	2.3	<1
Grapefruit, white, raw	21.3	<1	-
Lemon juice, fresh	1.4	14.5	4.9
Lemon, raw	<1	27.9	21.4
Orange juice, fresh	2.1	12	<1

Orange, raw	15.3	27.2	-
Pummelo juice, fresh	25.3	1.8	2.9
*per 100 g [fresh weight] or 100 mL [liquids]; 100 grams is equivalent to about 3.5 ounces; 100 mL is equivalent to about 3.5 fluid ounces.			

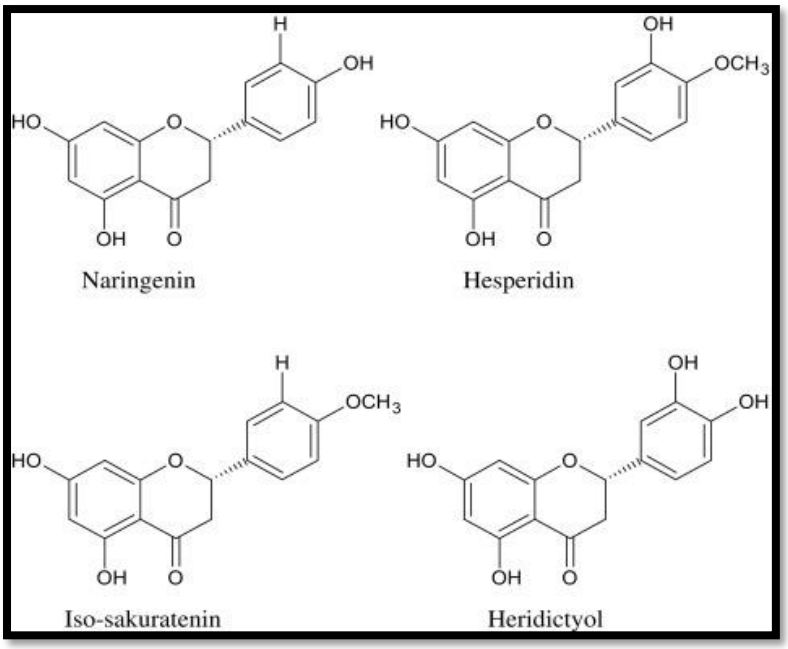

Fig.5: Structures of Flavanones

Metabolism and Bioavailability:

The bioavailability of flavanones depends on their absorption into the body fluids. After absorption, flavanones are rapidly and intensively metabolized by intestinal and liver enzymes [e.g., phase II metabolites] and available as metabolites in blood and urine [4]. The biological activity of metabolite may vary from its parent compuound.[5].

Detoxification pathway:

Flavonoids are recognized by the body as xenobiotics and undergo rapid metabolism first in the intestinal mucosa and then in the liver.

Phase II enzymes:

Flavonones are rapidly transformed by phase II detoxification enzymes to form methylated, glucuronidated and sulfated metabolites based on their structural characteristics [2]. The solubility of phenolic aglycones is increased by this pathway and facilitates the metabolite excretion in the bile and urine [11]. Free [unconjugated] aglycones like catechins alone are present in the bloodstream

[17]. The main metabolising enzyme is Catechol-O-methyltransferase [COMT], which cause methylation of the hydroxyl groups of flavonones, producing O-methylated flavonones. Studies says that subjects who has less eliminating capacity of green tea flavonoids are more benefited by its consumption [19].

Bindingto plasma proteins:

The bioavailability of flavonones is inversely proportional to their binding affinity to plasma proteins [21]. Lower the bioavailability, greater the binding affinity to plasma proteins. Aglycones have a limited bioavailability than glycosylated because glycosylation reduced binding affinity to plasma proteins. Glucuronidation facilitate the excretion of flavonones from the body [8].

Inhibition of CYP 3A4 by flavonoid-rich grapefruit

The most available CYP isoform in the liver and intestines is cytochrome P450 3A4 [CYP3A4][103]. Consuming of one grapefruit or 200 mL [7 fluid ounces] of grapefruit juice can irreversibly inhibit intestinal CYP3A4 [101]. Furanocoumarins [dihydroxybergamottin] are the most potent inhibitors of CYP3A4 in grapefruit.

Note: People taking medications with low bioavailability should avoid consuming Flavanones and containig foods during the treatment period [105].

Flavanone – Food interactions:

The physicochemical properties of flavonones affect the binding affinity and interactions of flavonones with food proteins, carbohydrates, and fats. Proteins in milk bound to flavonones can reduce their antioxidant capacity in vitro [102] and weaken the vascular benefits. Some carbohydrate-rich foods may increase the deglycosylation and absorption of flavonones by stimulating mucosal blood flow, gastrointestinal motility and colonic fermentation [106].

Radical Scavenging

Flavonones can reduce injury caused by free radicals by direct scavenging process. Free radicals oxidiseflavonones, which give more stable and less-reactive free.The main mechanism of flavonones in scavenging activity is higher reactivity of the hydroxyl group [105]

$$\text{Flavonoid (OH)} + \text{r(O)} + \text{RH},$$

Where, O - is an oxygen free radical and R - free radical.

Hanasaki et al.[106] found that flavonones such as Hesperitin, Naringin and Naringenin are good radical scavengers

and the scavenging mechanism of rutin is due to Xanthine oxidase enzyme inhibitor.

Future Research and Development:

As there are many side effects with the conventional therapy for treatment of ADPKD, flavanoids, are emerging as most effective way to treat ADPKD. The most important class of flavanoids is Flavanones. Flavonones are being mentioned in the research literatures over the past 10 years and many interesting and potential benefits have been identified. However, numerous works are being going on both in vitro and in silico, there is a need for further studies for elucidating the uses of

flavonones for improvement in human health. The research study on flavonones is little difficult because of the heterogeneity of the different molecular structures. Furthermore, limited amount of data is available to measure oxidative damage of flavanones in vivo and the measurement of end points remains difficult. More research is also going on to improve the analytic techniques to measure pharmacokinetics and pharmacodynamics. Most of the flavanones in therapeutic doses are safe, but flavonone overdose and prolonged usage side effects are still to be completely known.

As a result of numerous of reports on flavanones, molecular docking studies are required to isolate the therapeutic molecules and to know their uses in various diseases to improve human health system. Receptor level study of flavonones is the important area of future research in the treatment of acute and chronic diseases and also to know all the possible side effects. In this situation, there is a further need of research involving in vivo studies which will give a hopeful and safe flavanone for the future. in the present scenario flavanones containing foods are recommended, in the management of many diseases.

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