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Flavonoids, catching up with ACE-inhibitors and angiotensin receptor blockers to treat Diabetic Nephropathy?

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ABSTRACT

Worldwide, millions of people suffer from diabetes mellitus (DM) and this number is expected to rise in the near future. Despite adequate treatment, complications such as diabetic nephropathy (DN) are still common. DN is commonly treated with angiotensin converting enzyme inhibitors (ACEi's) or with angiotensin receptor blockers (ARB's). However, these therapies are not always effective in DN. Particularly in end stage renal disease (ESRD), ACEi's and ARB's are less effective and also a large fraction of patients do not respond or do not tolerate these drug classes.
Flavonoids are reported as natural compounds found in several dietary products with many similar effects as ACEi's and ARB's. Therefore the aim of this review was to compare flavonoids with ACEi's and ARB's and to see if flavonoids are a good add-on in the treatment of DN. Several studies have shown that flavonoids have similar effects as ACEi's and ARB's in the treatment of DN. They all can reduce proteinuria and prevent from ESRD by similar mechanisms like a reduction of inflammation, a reduction of reactive oxygen species (ROS) and a reduction of fibrosis. In specific comparative studies between a flavonoid and an ACEi or an ARB, flavonoids seemed to be at least as effective as ACEi's and ARB's. Furthermore, these studies showed that co-administration of a flavonoid with an ACEi or an ARB was more effective than monotherapy with one of the two. This means that co-administration could reduce the amount of people developing ESRD. However, there is not a complete consensus in scientific literature whether pharmacokinetic aspects of flavonoid would be favorable or not, though not many studies are carried out on this specific topic yet. Therefore, flavonoids could still be an important addition to the current therapy against DN when focused on co-administration with ACEi's or ARB's.

KEYWORDS
Diabetic nephropathy, flavonoids, ACE-inhibitors, angiotensin receptor blockers

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1. INTRODUCTION

Nowadays, diabetes Mellitus (DM) is getting more attention because approximately 415 million adults suffer from this disease worldwide and the expectation is that this number will rise to 642 million by 2040 [75]. DM can be roughly divided into type 1 and type 2 DM. [140]. Both are characterized with hyperglycemia and only the cause differs. Type 1 is characterized by an absolute deficiency in insulin secretion while type 2 is characterized by insulin resistance and an inadequate compensatory insulin response [122].

High glucose levels enhances the risk of different diabetic complications including diabetic nephropathy (DN). Next to high glucose levels these complications may be induced by an increase of oxidative stress and a decrease of endogenous antioxidants. [135]. DN can occur in both type 1 DM and type 2 DM, although in type 2 DM it is more frequent and in type 1 DM this complication is often more severe when it occurs [133]. DN is mostly treated with angiotensin converting enzyme - inhibitors (ACEi's) or angiotensin receptor blockers (ARB's). Although ACEi's and ARB's are considered first line therapy, these drugs often only delay the early progression of DN. They are less helpful in patients with an advanced form of DN or in patients suffering by end stage renal disease (ESRD) [126] [41]. In an ESRD phase, kidney transplantations are often necessary, which is often difficult due to the lack of donors [32]. Furthermore, ACEi's and ARB's cannot be tolerated well by every patient with DN. They both can give side effects like a cough stimulus that cannot be treated with antitussive products [100]. This is occurring in more than 30% of patients using ACEi's or ARB's [111]. Other side effects of ACEi's and ARB's are angioedema or idiosyncratic reactions like hepatitis, alopecia, hypotension and hyperkaliemia [105] [81] [64]. Besides the side effects, ACEi's and ARB's are also expensive because they are synthetic and therefore, a cheaper therapy would be agreeable [96].

Flavonoids are natural compounds that are used for centuries in traditional medicine all over the world and they are still being used in this kind of medicine [70] [97]. Next to this fact many flavonoids are already present in low dosages in daily diets of many people [23]. Since a few years, flavonoids are getting more attention in scientific literature. They should have beneficial properties in several diseases and complications including DN. Therefore, this review will discuss the effects of flavonoids in comparison with the effects of ACEi's and ARB's on DN to see if flavonoids could be a useful addition or replacement of ACEi's and ARB's in the treatment of DN.

2. PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY

DN can be divided into three clinical phases; microalbuminuria, macroalbuminuria and ESRD and it is worldwide the greatest contributor of chronic kidney disease (CKD) [1]. Patients are diagnosed with microalbuminuria when the amount of albumin in their urine is higher than 30 mg/24 h [1]. When the amount of albumin in the urine increases to more than 300 mg/24 h a patient is diagnosed with macroalbuminuria [93] and when the filter capacity of the kidney's decreases that much that it has reached the point that the rest of the body suffers extremely from it, the phase is called ESRD [1]. In the next section several molecular causes of DN are discussed.

2.1 Insulin insensitivity

One of the earliest factors that can be an indication for DN in diabetic patients is insulin insensitivity [15]. Insulin is a hormone that supports tissues like muscles and the brain to pick up glucose from the blood and it is produced by the β-cells in the islets of Langerhans [125] Due to hyperglycemia, a high amount of insulin is released by the β-cells resulting in hyperinsulinemia. Inflammatory processes can induce insulin resistance for example via the inflammatory pathways that contain nuclear factor kappa-light-chain-enhancer of activated B cells (Nf-κB) [38]. Nf-κB is responsible for the induction of various inflammatory pathways by enhancing the expression of several inflammatory markers [12]

2.2 Onset of ROS by forming of AGE

An elevated glucose level in the blood can also induce damage to the kidneys via the forming of reactive oxygen species (ROS). ROS can inter alia be formed by advanced glycation of end-products (AGE's). AGE's can be formed when lipids, amino acids, nuclear acids or proteins like hemoglobin, become non-enzymatic glycated via a reduction of sugars or aldehydes [30]. AGE's can also be formed by metabolites of the glycolysis like the compound methylglyoxal that can react with free lysine groups of proteins leading to AGE's [118] [138]. After AGE's are formed, they generate ROS by reacting with proteins like nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) of the mitochondrial respiratory cycle [29][51]. A high amount of ROS can also be formed in the kidney cells in the respiratory cycle during the degradation of the excess of glucose [21].
In addition to the generation of ROS, AGE can also bind to the extracellular receptor of AGE (RAGE) [130]. Via RAGE, ROS can activate Nf-κB by first triggering NADPH-oxidases [151]. Furthermore the binding of AGE to RAGE can induce nitro-oxidative stress, because the protein induced NO-synthase (iNOS) is upregulated resulting in the production of NO which can be reactive in high amounts. [131].

2.3 RAAS system

Another reason microalbuminuria occurs is due to an imbalance of the renin-angiotensin-aldosterone system (RAAS). Renin that is produced by the kidney can convert angiotensin which is produced in the liver into angiotensin I in the blood, whereby angiotensin I can be converted into angiotensin II by the angiotensin converting enzyme (ACE). Angiotensin II can bind to the angiotensin II receptor in the efferent arteriole in the kidney and induce vasoconstriction, but it can also release the hormone aldosterone from the adrenal cortical what can contribute to a higher blood pressure by increasing the water and sodium resorption. Therefore, due to angiotensin II, the blood flow in the kidneys will be slowed down and as a result the glomerular pressure will be increased [124]. This glomerular hypertension can induce oxidative stress in the glomerulus

resulting in endothelial dysfunction, which can trigger inflammatory pathways inter alia via Nf-κB [60].
Besides the role of RAAS in the pathophysiology of diabetic nephropathy it often also plays an important role in the development of DM because due to hyperglycemia, proteins of RAAS are more expressed what can lead to an impaired insulin sensitivity both in the β-cells of the pancreatic islets and in the target tissues [84] [158].

2.4 Fibrosis

Renal fibrosis can also be a hallmark for DN via the transcription growth factor β (TGF-β) and connective tissue growth factor (CTGF) [141] [63]. The expression of TGF-β can become upregulated by Nf-κB [12] [78]. TGF-β can upregulate the expression of CTGF for example via SMAD or protein kinase C (PKC) signaling. CTGF can generate extracellular matrix (ECM) proteins like collagen and fibronectin [56]. This fibrotic process in DN often reveals itself in pathological features to the podocytes of the kidney. Podocytes function as a filter in the kidney and therefore, they can prevent from proteinuria [56].

2.5 Dysregulation of the lipid metabolism

A dysregulation of the lipid metabolism is another important factor in the development of DN. In DN peroxisome proliferator-activated receptor (PPARα) is often deficient, thereby inducing circulating free fatty acids and triglycerides [114]. PPARα is able to modulate the lipid metabolism and inflammation in such a way that it reduces the low-density lipoprotein (LDL) levels and elevates the high-density lipoprotein (HDL) levels. HDL is able to suppress the expression of inflammatory cytokines [34]. DN is associated with a defect receptor pathway for LDL what can result in an accumulation of lipids in podocytes [154]. A high amount of cholesterol in the blood also seems to have a linkage to the development of DN because it can lead to a decrease of the glomerular filtration rate (GFR) [107].
In the pathophysiology of DN another process also plays an important role namely lipid peroxidation. During lipid peroxidation polyunsaturated lipids can be damaged by ROS because poly-unsaturated lipids have a prosperity to react with ROS. One of the byproducts of this reaction is malondialdehyde which functions as a biomarker of lipid peroxidation [123] [40].

3. INTERVENTION OF ACEI'S AND ARB'S ON PATHOPHYSIOLOGICAL PATHWAYS OF DN

Currently at least 10 ACEi's and 7 ARB's are marketed in the United States [64]. DM type 2 is treated with both ACEi's and ARB's but type 1 is only treated with ACEi's due to a lack of data [92]. In the last decades, various clinical studies have demonstrated that ACEi's can reduce the progression of DN induced by type 1 DM [25][90][110][137][142]. In patients with type 2 DM and DN, it has been shown that ACEi's can reduce the progression of DN too [58][74][119]. With regard to the ARB's, in type 2 DM numerous studies are also performed that gave a reduction in the progression of DN [10][19][76][91][95][116][121][152]. Besides for the independent testing of ACEi's and ARB's, there are also a lot of studies performed that tested both in the same time [11][77][85][104]. Surprisingly, those studies have been carried out both in type 1 and type 2 DM in contrast to the monotherapy studies. In all of the comparison studies the progression of DN was lowered and the blood pressure control was improved compared to monotherapy with ACEi's or ARB's. With regard to the mechanisms of ACEi's and ARB's also several studies were carried out in DN models and the main results are discussed below.

3.1 Molecular aspects of ACEi's

First of all, the ACEi's consist of three main subgroups distinguished by their chemical structures. Namely the sulfhydryl-containing ACEi's (**captopril**), the phosphinyl group containing ACEi's (**fosinopril**) and the ACEi's containing a carboxyl moiety (**enalapril**) [20]. All of the ACEi's block the conversion of angiotensin I into angiotensin II by ACE and inhibit the degradation of bradykinin [66]. Bradykinin can enhance the vasodilatation by binding to the B1 endothelial receptor leading to a NO-release and bradykinin is also degraded by ACE [59]. Some specific effects of different ACEi's on the pathophysiology of DN are listed below.

3.1.1 Sulfhydryl-containing ACEi's

Captopril was the first discovered ACEi's that could be orally administered [43]. In mice it was proven that captopril decreases the albuminuria levels, inhibit glomerulosclerosis and decrease the macrophage infiltration [153][82]. Captopril can also enhance the insulin sensitivity [13]. In addition captopril is able to inhibit elevated levels of tumor necrosis factor α (TNF-α), NO, renal malondialdehyde and it can prevent glutathion depletion in diabetic rats [54]. In a study of Huang and colleagues captopril was capable to inhibit RAGE expression in normal rat kidney fibroblasts [73]. In another study captopril inter alia improved the lipid profile [7]. Furthermore, in dogs, captopril was able to reduce renal fibrosis [127]. Because of all these reasons, captopril is regarded as a renoprotective compound [69].

3.1.2 Phosphorus-containing ACEi's

In a study carried out by Huang and colleagues, ***fosinopril*** seemed to improve the renal function in DN by depressing chemerin and therefore VEGF-expression in rats [72]. Chemerin is an adipocytokine that is involved in the glucose and lipid homeostasis [62]. Serum chemerin levels are strongly associated with renal dysfunction in diabetic patients and it functions therefore as a biomarker [16] [71]. Vascular endothelial growth factor (VEGF) is proven to be lightly increased in the early development of DN because it can stimulate the proliferation of vascular endothelial cells

and therefore stimulate the angiogenesis in DN patients [117]. In a study with humans fosinopril also improved the lipid profile [42]. Furthermores, fosinopril diminishes proteinuria, tubulointerstitial fibrosis, and glomerular hypertrophy[143]. In addition. fosinopril is able to reduce oxidative stress and improve insulin sensitivity[135] [8].

3.1.3 Dicarboxyl-containing ACEi's

In a study of Cucak and colleagues ***enalapril*** not only seemed to reduce the albuminuria but also seemed to restore the disbalance of T-cells and M1-like macrophages induced by DN in an early stage in db/db mice [37]. Patients with albuminuria lose a high amount of leukocytes due to an accumulation in the kidney [33]. In another study enalapril could normalize the blood pressure in diabetic rats and therefore almost prevent the onset of DN. [14]. Wagner and colleagues found that enalapril could improve the cell mass of the β-cells in mice [55]. They saw in the same study an increase in the glucose regulation protein adiponectin also and an increase in the expression of the glucose transporter 2 (GLUT2) which can transport glucose without support of insulin. Furthermore enalapril is able to protect vascular endothelium from ROS, to attenuated lipid accumulation and to inhibit fibrotic processes [83] [149] [132].

3.2 Molecular aspects of ARB's

ARB's can block the function of angiotensin II by blocking the angiotensin receptor without involving ACE [65]. Some examples of ARB's are **losartan** and **valsartan**. Specific effects of ARB's with regard to DN are listed below.

3.2.1 Losartan

Losartan is capable of reducing the macrophage infiltration, to inhibit the TNF-α expression and to reduce the renal glomerular and perivascular fibrosis in Zucker diabetic fatty rats [24]. Losartan is also able to ameliorate RAGE and MCP-1 promoters in mesangial cells of db/db mice [120]. In addition losartan is proved to modulate the expression levels of proteins involved in the PI3K-AKT-mTOR pathway in a beneficial way in a study carried out in rats [101]. The PI3K-AKT-mTOR pathway, which can be activated by angiotensin II, can also lead to some of the features of DN such as cell hypertrophy and matrix production [101]. Another study shows that Losartan could neutralize oxidative stress and decrease insulin resistance in type 2 DM patients mainly via the PI3K pathway [113]Furthermore, losartan blocks the progression of early DN in American Indians with type 2 DM [146]. This same study also showed that Losartan cannot be used to prevent American Indians from DN. There is also evidence that losartan is able to improve lipid levels [53].

3.2.2 Valsartan

Valsartan not only reduces albuminuria but can also stop the progression of glomerulosclerosis in mice with DM type 2 via a reduction in podocyte injury and via a lowering of the renal oxidative stress and inflammation [156]. In particular TGF-β1 and type IV collagen were inhibited in this study. In another study valsartan was also capable to reduce the Nf-κB activity, MCP-1 expression and macrophage infiltration in humans [39]. In addition a study carried out by Wang and colleagues in mice with DN, valsartan was able to prevent an increased expression of the pro-fibrotic growth factor CTGF and the pro-inflammatory cytokine TNF-α [145]. Furthermore, they saw a decrease in the lipid accumulation in the kidney.

4. INTERVENTION OF FLAVONOIDS ON PATHOPHYSIOLOGICAL PATHWAYS OF DN

Flavonoids are a group of natural mostly dietary polyphenolic products that are present in all kinds of fruit, vegetables, beverages, grains and herbs [23]. There are at least more than 5000 different flavonoids identified [49] and they can roughly be separated into six different classes of flavonoids like flavonols, flavones, flavanones, flavan-3-ols (flavanols), anthocyanins and isoflavonoids. These six classes almost all have the same chemical structure [49]. (Figure 1)

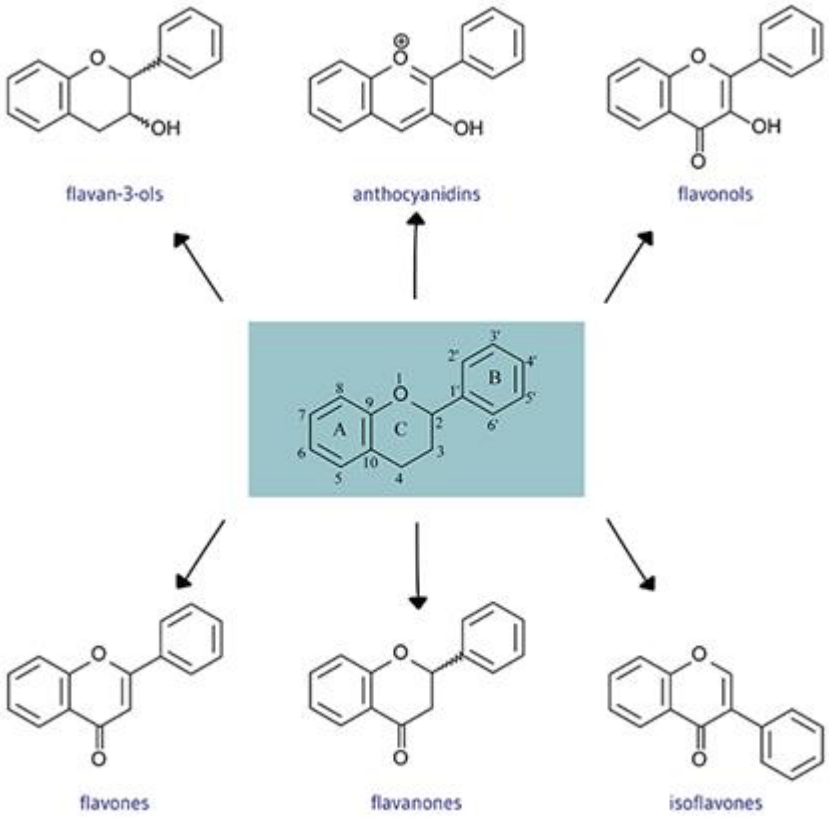

Figure 1: Basic structure of flavonoids and specific structures of six classes of flavonoids [103]

Through the years, a variety of studies have been performed to examine the effects of flavonoids on human health. Several animal studies have also been published about the effect of flavonoids on DM with DN. Even a single clinical trial was carried out with the isoflavonoid genistein with promising effects [52]. In the next section from each of the flavonoid groups, some compounds will be discussed on their effects on the pathological features of DN.

4.1 Flavonols

The flavonol **quercetin** may be the most wide studied flavonoid. It is present in many human nutrition sources like grapes, citrus rinds and onions and it is also available as a dietary supplement without prescription [67] [4]. In a study of Lai et al., quercetin was able to reduce the amount of excreted albumin in the urine of diabetic rats. Quercetin could also inhibit the overexpression of

TGF-β and CTGF in diabetic rats and thereby inhibiting the fibrosis process [86]. In another study DN was induced in mice and they were then treated with quercetin [61]. The results of this study were inter alia a reduction in proteinuria, plasma glucose, triglycerides, creatinine and in mesangial matrix expansion together with a reduction in ROS production. Regarding to the oxidative stress, quercetin is able to combat with ROS in diabetic pregnant rats in different ways [17]. An example for this is via a direct interaction with ROS and thereby neutralizing it, via the forming of hydroxyl radicals due to a chelation of iron ions or via a directly interaction with lipid peroxyl radicals scavengers during the lipid peroxidation [17]. In a study with human mesangial cells, quercetin was also able to reduce the expression of Nf-κB [147]. Next to an effect on different kinds of inflammatory pathways, quercetin might also have an interaction on RAAS resulting in a decrease of expression of the angiotensin I receptor and of aldosterone [94].

4.2 Flavones

The flavone **baicalein** can be found in many natural products like the skullcap or golden root (*Scutellaria baicalensis Georgi*) or in fruits of the *Oroxylum indicum* [87]. Baicalein seemed to be able to strongly scavenge ROS in murine cells [87]. A second function of baicalein is the suppression of Nf-κB and therefore also a decrease in expression of iNOS, TGF-β and an improvement of the renal structure was observed in type 2 diabetic rats [5]. In another study, baicalein seemed to reduce the amount of AGE in insulin deficient and insulin resistant diabetic rats [47]. Another flavone named **chrysin** that can be found in numerous plant extracts and honey [26], also seemed to reduce the pathologic features of DN. Ahad and colleagues reported that chrysin suppresses the expression of TGF-β, fibronectin (a key player in the fibrosis process) and collagen-IV in type 2 diabetic rats [6]. In another study chrysin was capable to reduce epithelial to mesenchymal transition (EMT) mediated tubulointerstitial fibrosis [80]. Chrysin was also able to reduce oxidative stress in diabetic rats [48]. AGE-forming, NO-generation and lipid peroxidation were diminished as well. In this study the flavone **luteolin** also decreased the AGE-formation, NO-generation and lipid oxidation [48]. Luteolin is widely studied in DM and can be isolated from the plant L. japonica [115]. With regard to DN, luteolin can enhance the antioxidant levels in the kidney like super oxide dismutase (SOD), carried out in rats with induced type 1 DM, partly by the fact that it has an antioxidant function by itself [144]. Besides, luteolin is able to reduce the creatinine levels in the blood plasma, but luteolin can also block Nf-κB, iNOS, cyclooxygenase-2 (COX-2), TNF-α and interleukine-6 (IL-6) in mouse peripheral macrophages [27].

4.3 Flavanones

The flavanone **Naringenin** is also a potential candidate in the therapy for DN and it can be found in different vegetable sources like tomatoes, grapefruit and lemon. In a study of Mulvihill et al., naringenin was capable of reducing insulin resistance in mice [108]. In a study of Tsai et al. naringenin was able to suppress the expression of cytokines like MCP-1, TNF-α and fibrotic factors like fibronectin and TGF-β1 in mice [139]. Furthermore, naringenin was able to block the Nf-κB activation and it was able to lower the renal PKC. The flavanone **rutin** which can be converted into the flavonol quercetin dependent on the temperature [36] showed a decrease in AGE levels, the plasma creatinine levels, the amount of protein excreted in the urine, the expression of TGF-β_1 and related proteins like SMAD2/3 and CTGF in a study of Hao et al. carried out with rats [64]. In this same study the plasma glucose levels were also declined. Before this study was performed, it was discovered by Kampkotter et al. that rutin had an antioxidant function in the model organism Caenorhabditis elegans although not that strong as quercetin (62,6% versus 89,8% for the2,2 diphenyl-1-picrylhydrazyl radical) [79] [150] [36].

4.4 Flavanols

The flavanol (+)-**catechin** can be found for example in dietary products like green tea [82]. (+)-catechin can have an antioxidant effect at dietary dosages and therefore, it could be helpful in the treatment of DN [45]. However, when the dosages are higher, (+)-catechin can have a pro-oxidantive effect [57]. In a study of Zhu and colleagues, (+)-catechin seemed to have the potential to inhibit AGE formation and to stop the inflammatory pathway by trapping the compound methylglyoxal in type 2 diabetic mice [157]. In another study carried out by Chennasamudram et al., (+)-catechin reduced albuminuria, plasma creatinine concentrations, fibronectin concentrations and the lipid peroxidation in diabetic rats [28].

4.5 Anthocyanins

Anthocyanines are responsible for the red blue and purple colors of many natural products like blueberries, blackberries, cherries, pomegranates and radishes [9]Not many studies researched the effect of anthocyanins on DN. However, anthocyanins can modulate the cholesterol metabolism in high glucose human kidney cells (HK-cells) and it is also reported that anthocyanines are able to neutralize ROS and enhance the cholesterol efflux by activation of PPARα and liver X receptor alpha (LXRα) [44]. LXR has as main function to maintain the cellular cholesterol homeostasis. Furthermore, anthocyanins can inhibit Nf-κB in such a way that it cannot transfer anymore to the nucleus. In addition, anthocyanines are able to block the production of inflammatory cytokines like MCP-1, intracellular adhesion molecule 1 (ICAM-1) and TGF-β_1 as well [44]. However, less is known about the structure- activity- relationships of the anthocyanins [44].

4.6 Isoflavonoids

The isoflavonoids are abundant in traditional Chinese medicine and can be found inter alia in the roots of the *Pueraria Lobata* [22]. They are characterized by the fact that their phenyl group is not attached to the second position next to the oxygen but to the third position in contrast to the other flavonoid groups. Through the years several isoflavonoids have been studied. **Genistein** is the most important member of the isoflavonoids and it can improve insulin resistance and reduce the oxidative stress due to an increase of the GSH levels. Genistein is also capable of reversing the glomerular damage due to an inhibition of TGF-β, type IV collagen and fibronectin in rats [112]. In addition genistein can diminish the Nf-κB expression and it can increase the level of SOD and catalase in a murine macrophage cell line [31]. In a study of Montenegro et al. genistein was able to decrease the plasma levels of ACE in rats [106].

5. COMPARISON BETWEEN ACEI'S, ARB'S AND FLAVONOIDS

5.1 Similaritive effects of ACEi,s, ARB,s and flavonoids in DN

Generally, ACEi,s, ARB's and flavonoids share many features that can be useful in the therapy for DN. Almost all ACEi's ARB's and flavonoids discussed above are able to reduce the albuminuria because they can inhibit the inflammatory processes in the kidneys by reducing the amount of AGE and by blocking Nf-κB for example. (table 1)

Table 1: A summary of the most important effects of the different flavonoids, ACEi's and ARB's on the pathophysiological pathways in DN.

	Reduction of insulin insensitivity	**Anti-oxidant function**	**RAAS inhibition**	**Reduction of renal fibrosis**	**Reduction of dysregulation of lipid metabolism**	**Additional properties**
ACEi's						
Captopril	+	+	+	+	+	*Prevent gluthation depletion*
Fosinopril	+	+	+	+	+	
Enalapril	+	+	+	+	+	*Restore immunological disbalance*
ARB's						
Losartan	+	+	-	+	+	
Valsartan		+	-	+	+	
Flavonols						
Quercetin	+	+	+	+	+	
Flavones						
Baicalein	+	+		+		
Chrysin		+		+	+	
Luteolin	+	+		+	+	
Flavanones						
Naringenin	+			+		
Rutin	+	+	+	+		
(+)-catechin		+		+	+	*Pro-oxidative at high doses.*
Anthocyanins	+	+		+	+	
Isoflavonoids						
Genistein	+	+	+	+		

"+" = significant improvement. "-" = not a significant improvement or deterioration. " " = not known yet

However, so far, only publications that report the single mechanisms and functions of ACEi's, ARB's and flavonoids are described. Some studies are also known that compare the different (potential) therapies; ACEi's or ARB's and flavonoids . In a study of Ertürküner and colleagues the effects of the ACE-inhibitor perindopril and the flavonoid (+)-catechin on the mesangial matrix and the podocytes

were compared in diabetic rats [50]. They found that a co-administration of (+)-catechin and perindopril was more effective than a single administration of one of the two. In another study, (+)-catechin had similar renoprotective effects as enalapril in diabetic rats [28]. In this study (+)-catechin had comparable inhibiting effects on lipid peroxidation, expression of fibronectin, on the plasma creatinine and on the creatinine clearance. The authors of this study also suggested to co-administer (+)-catechin with enalapril to enhance the reduction of albuminuria. A study carried out by Xu et al. compared the renoprotective effects of the flavone breviscapine with enalapril and they also found that a co-administration of both compounds gave a stronger reduction in glomerulosclerosis than monotherapy could gave [148]. In addition, a study performed by Zhong and colleagues compared the therapeutic effects of the ARB Losartan with the isoflavonoid compound puerarin on DN in diabetic rats [155]. Many therapeutic effects were similar like the improvement of the kidney hypertrophy, proteinuria and the podocyte foot process erasure. Interestingly, in this study puerarin was able to suppress the oxidative stress in the kidneys more than losartan could. These studies also indicate that a co-administration of an ACEi or ARB together with a flavonoid could be beneficial for patients with severe DN like ESRD, because co-administration makes it possible to get a stronger reduction of the pathological symptoms of DN than with monotherapy. Co-administration could be applied in for example ESRD because monotherapy in ESRD is often not sufficient to improve the kidney function.

5.2 ACE-inhibiting and pharmacokinetic effects of flavonoids

In a study of Shukor and colleagues the structure activity relationships of different compounds to inhibit ACE were examined. In this study the IC_{50} of the ACE-inhibitor lisinopril was 1,00 nM while the flavone apigenin had only an IC_{50} of 0,667 mM, the flavanone rutin had an IC_{50} of 0,472 mM, the flavonol quercetin had an IC_{50} of 0,415 mM and the flavanol epicatechin had an IC_{50} of 1,381 mM. Rutin inhibited ACE only via hydrogen bonds with amino acids in the active side of ACE but not with the zinc ion of ACE in contrast to ACEi's. Quercetin and epicatechin were able to form an interaction with ACE via both the zinc ion of ACE together with amino acids of ACE. The study also showed that the presence of a catechol group on the flavonoid, seemed to increase the potency to inhibit ACE. Therefore, from all flavonoids, quercetin seemed to have the most ACE inhibiting capacity. Although none of the flavonoids was as effective as the ACE-inhibitor lisinopril, they were all able to inhibit ACE in vitro according to this study [128]. However, in a study carried out by Neto-Neves et al. the flavonol quercetin did not have any effect on ACE-inhibition in vitro or in vivo when it was long-term administered intraperitoneally in rats [109]. Surprisingly, several human in vivo studies with flavonoids showed a decrease of the blood pressure [109][46]. A study of Brasil et al showed that a flavonoid extract including quercetin and rutin, from *Carica Papaya* gave a similar antihypertensive effect due to ACE-inhibition than enalapril [18]. Presumably, ACE-inhibition by flavonoids plays a role in the decrease in blood pressure but next to other mechanisms like a reduction of oxidative stress, a decrease of AT-I expression, a modulation of renal function and an improved endothelial function [89].

Regarding to the bioavailability of the three different groups of compounds the differences are higher. For example the oral bioavailability of captopril is 70%-75% [99] and the oral bioavailability of Losartan is 32,6% [129]. However, the bioavailability of flavonoids seemed to be very low though most of the flavonoids are present in daily diets too [68]. For example the bioavailability of the flavonol quercetin is in pigs less than 1 percent [3]. In healthy men a dose of 1,095mg quercetin gave a blood concentration of 2,33 µM after 10 hours and after 24 hours the concentration was turned to baseline [88]. In 2005 Manach and colleagues made a ranking of the bioavailability of the different groups of flavonoids. Isoflavones seemed to have the best bioavailability of all flavonoids and anthocyanidines the worst. After the isoflavones the flavanols, were the best, then the

flavanones and the flavonols have the second to last bioavailability [98]. On this moment several studies are carried out to improve the bioavailability of flavonoids for example via the development of devices that can transport flavonoids like quercetin or genistein in a higher concentration into the tissues [36] [35].

Coming back on quercetin, the low bioavailability and the fact that it can decrease blood pressure could also be explained by the fact that it accumulates near to membranes after repeated intake. Due to this accumulation, a higher concentration of quercetin could be reached in the intestine than in the blood [2]. ACE is known to be a membrane bound enzyme [102]. This could be a reason that in the study carried out by Neto-Neves et al. no significant effect of quercetin on ACE was perceivable because quercetin was intraperitoneally administered while in the other studies quercetin was orally administered [46].

5.3 Additional properties of flavonoids

Except for the functions flavonoids carry out on the described pathological pathways of DN that are the same as ACEi's and ARB's , flavonoids might also have other protecting functions. For example, in a study of Tang et al. both rutin and captopril were compared to see if those compounds had similar protecting effects on fibrotic processes in DN. In this study rutin had many the same properties as captopril except for the fact that rutin was able to decrease the chance of mesangial cell hypertrophy due to a G1 arrest in contrast to captopril. Captopril had no significant effect on the cell cycle in this study [134]. Next to the beneficial effects flavonoids have on DN, many flavonoids have, just like most ACEi's and ARB's, favorable effects on the development of other diabetic complications as well. Examples are diabetic neuropathy, diabetic cardiopathy and diabetic retinopathy [136]. This means that flavonoids might also be used to treat several diabetic complications in the same time. Furthermore, flavonoids are not characterized with severe side effects, for as far as they are studied at the moment in contrast to ACEi's and ARB's. This last statement, supports also a co-administration of flavonoids with ACEi's or ARB's because it probably will not lead to more side effects than monotherapy.

CONCLUSION

Until now many studies have been carried out with flavonoids. Those studies show many promising features when compared to studies with ACEi's and ARB's. Although flavonoids seem to give several beneficial effects as ACEi's and ARB's, a co-administration of flavonoids and ACEi's or ARB's will be a better therapy than only ACEi's, ARB's or flavonoids because pathological symptoms decrease more during co-administration than when only monotherapy is administered. Especially for DN patients in an advanced stage, this co-administration could be an important addition to the DN therapy. This may lead to a reduced need of donor organs in future worldwide and therefore, flavonoids could also be part of a solution to the donor problem worldwide. Furthermore, flavonoids couldn be a good alternative for patients who are using ACEi's or ARB's and are suffering from side effects. Pharmacokinetic aspects may not be completely favorable at this moment, not many studies on this topic have been carried out yet though. Because of all these reasons, flavonoids can still become an important addition in the therapy of DN.

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