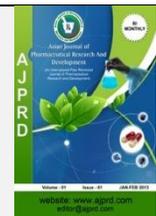


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Review Article

## Investigations on Kaempferol, Quercetin and Other Flavonoids in Aquatic Plants of Iraqi Marshlands-I

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### ABSTRACT

Aquatic plants are versatile source of phytochemicals that are of significant biological influences particularly, the flavonoids and their glycosidic derivatives distributed in different plant parts including fruits, seeds, leaves, flowers, stem, roots and rhizomes. Most of the reported biological influences are reported to be expressed by quercetin, kaempferol, isorhamnetin, and their glycosidic derivatives, particularly, rutin. In this survey, we summarized the reported flavonoids types, content and factors affecting their extracts contents of three aquatic plants Nuphar, Najas and Nymphaoides detected in the Iraqi central marshlands, in provenance of Thi-Qar. Surveying the phytochemical investigations regarding Nuphar species of reported abundance of polyphenolic compounds content including identified and quantified phenolic acids, flavonoids like flavonols and flavonones, particularly, in their leaves. However, flavonoids/their derivatives types and quantities in various parts extracts are not reported to the extent of our knowledge although they are presumed to contribute to the reported biological influence of the plant on one hand. On the other hands, regarding Najas species, few reports have identified the existence of flavonoids as well as other phenolic compounds, although, total quantification to the phenolic compounds, flavonoids and tannins are reported rather than identifying the individual flavonoid in the plant extracts. Only single report demonstrates the total phenolic, flavonoids and tannin contents of ethyl acetate extract of Najas minor according to our survey. Regarding Nymphaoides species, the extraction level flavonoids as lipophilic compounds as well as their much polar glycosidic derivatives is depending on the solvent polarities. In general, in most of Nymphaoides species the ethanolic extract quercetin, methylquercetin and kaempferol flavonoids/their derivatives are identified individual flavonoids/quantified to be more than one fold of that in the aqueous extracts. Finally, the manner/position of glycosylation as well as glycosides sugar residues acylation vary among the Nymphaoides species. In general, single 3-O- or di 3,4'-O-glycosylation pattern is noticed in kaempferol, quercetin and isorhamnetin. The multiply diverse glycosylation, methylation as well as acylation pattern of Nymphaoides species flavonoids may explain their identification in various plant part/extracts besides the variation in their biological activities potentials.

**Key words:** Nuphar, Najas, Nymphaoides, Aquatic, Plants, Quercetin, Kaempferol.

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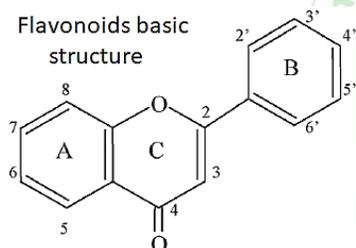
### INTRODUCTION:

Polyphenolics are naturally occurring plant secondary metabolites detected in almost all plant organs including fruits, roots, flower, leaves even in vegetables. Their remarkably interesting multiple pharmaceutical as well as therapeutic potentials against various health anomalies including cancer as well as cardiovascular diseases<sup>[1-6]</sup>. In fact, polyphenolic/phenolic compounds is a huge group of plant secondary metabolites

that approaches eight thousands compounds of simple or complexed structures made of one aromatic ring with one or more phenolic hydroxyl groups constituting phenolic acids, flavonoids, coumarins, tannins, phytochemical classes etc. according to their chemical architecture mostly biosynthesized

through shikimic acid pathway<sup>[7-10]</sup>. Flavonoids constitutes a characteristic class of polyphenolic compounds, widely distributed in vegetables and fruits especially the edible ones

<sup>[11, 12]</sup>. They are fundamentally built of fifteen carbon two aromatic ring skeleton of three carbons C6-C3-C6, however, in some cases their sugar as well as organic acids conjugated metabolites are also identified as their major derivatives conferring medicinal/therapeutic potential to their plants particularly the antioxidant activity <sup>[7, 11-14]</sup>. Chemically, flavonoids are classified according to the number as well as the arrangement of their structural carbons in to flavonols, flavones, flavan-3-ols, anthocyanidins, flavanones, isoflavones, etc. <sup>[10]</sup> mostly abundant in edible flower conferring them their health beneficial effects <sup>[15]</sup>. Flavonoids are of considerable stability along with tremendous structural diversity as they are structurally <sup>[16]</sup>, hence, functionally varies according to the saturation status of the oxygen heteroatom ring C at carbons C2 and C3 besides the pattern of rings A and B hydroxylation, methoxylation and glycosylation <sup>[17]</sup>. Consequently, the number as well as the location of the multiple OH groups determines their biological influences <sup>[18]</sup>. For example, hydroxylation at ring B, C3' and C4' hydroxylation confer capability of flavonoids participation in redox effect <sup>[19]</sup>, however, hydroxylation at ring C, C3 position contributes to their enzymes inhibitory influences <sup>[20]</sup> as they target mitochondrial sites, besides, C3 hydroxyl group acetylated derivatives processes caticholes protective influence <sup>[21]</sup>. In addition, the hydroxylation at ring A, C5 and C7 positions contributes to their weak acidity due to ring C, C4 carbonyl intramolecular H-bonding <sup>[21]</sup>.



### Some Biological Influences of Flavonoids:

Both nutritive and non-nutritive flavonoids particularly in plant flowers exhibit various biological influences besides their famously known antioxidant activity including protective influences against prolonged health conditions cancer, cardiovascular diseases, inflammation, diabetes, hepatic toxicity, obesity, and neurodegenerative disease particularly quercetin and its derivatives, besides, their inhibitory effects against broad spectrum of mammalian enzymes involved in cell proliferation, platelets aggregation, inflammation and immune response such as topoisomerase II inhibition influences of genistein, (–)-epigallocatechin gallate and catechins mediated anticancer influence <sup>[22-41]</sup>. In addition, flavonoids can inhibit various enzymes such as xanthine oxidase, protein kinase C, phosphodiesterase (like PDE-4), 5 $\alpha$ -reductase and protein tyrosine phosphatase 1B (PTP1B) enzymes <sup>[42-51]</sup>. In this regard, isoflavones and their derivatives are considered as effective as effective pharamcophor for the design of effectively powerful 5 $\alpha$ -reductase enzyme inhibitors <sup>[52]</sup> although many other common flavonoids are also recognized as inhibitors to this enzyme for treatment of androgenetic alopecia besides their anti-inflammatory as well as insulin resistance counter acting influences <sup>[53]</sup>. Moreover, flavonoids can exploit

microbial growth counteracting effect, antiulcer, antispasmodic, antiphotoaging as well as antiallergic activity <sup>[54-58]</sup>. Furthermore, colorful plant compounds including flavonoids, catechins, anthocyanins and proanthocyanidins along with non-colored flavonoids can regulates cellular signaling, growth, differentiation as well as survival pathways and other critical pathophysiological pathways explaining their apoptotic, cytotoxic influence in addition to chronic diseases curative effects <sup>[59-63]</sup>. Interestingly, flavonoid glycosides are also health beneficial substances possess <sup>[45, 46, 47, 64, 65]</sup> such as Quercetin-3-O-(2''-galloyl)-L-rhamnopyranoside that exhibits its anti-inflammatory influence via TNF- $\alpha$ -activated NF- $\kappa$ B-induced inflammatory mediator synthesis inhibition <sup>[66]</sup>. Vitamin as well as plants polyphenolic compounds including flavonoids are of potent antioxidant capability, thus they are useful adjuvant therapy to counteract osteoporosis <sup>[67]</sup>.

Generally, plants flavonoids have potent antioxidant capacity<sup>[68]</sup> mediated through one or more mode of actions including metal trapping (chelation) and/or scavenging of oxidative stress resulted free radicals (quenching of the reactive oxygen species) <sup>[45, 69-76]</sup>, or regeneration of the membrane bounded antioxidants <sup>[77-79]</sup>. Hence, inhibiting tissues lipid peroxidation through peroxy radical neutralization, explaining the principle antioxidant influences of fruits and vegetables <sup>[72-75]</sup>. Rutin for example has an antioxidant IC<sub>50</sub> of 25.8  $\mu$ g/mL against the pro-oxidant iron II <sup>[80]</sup>. Flavonoids of the aquatic plant *Nasturtium officinale* is one of the fundamental antioxidant components of the plant besides beta-carotene <sup>[81, 82]</sup>, thus, many of the flavonoids biological influences are significantly correlated to their potent antioxidant effect <sup>[83]</sup>. In fact, the flavonoids/flavonols antioxidant potential contribute to most of their therapeutic potential as it inhibit DNA oxidative damage by the reactive oxygen compounds like hydrogen peroxide or reactive oxygen species like singlet oxygen generated by radiations including harmful UV radiation <sup>[84]</sup>, besides, protecting body tissues against chronic diseases <sup>[85]</sup> such as tumor development as well as cardiovascular tissues through a similar mechanism <sup>[86-88]</sup>. In addition, it is necessary to note that the flavonoids reported tissue/organ protection effects such as kidney protection in diabetic models through prevention or controlling nephropathy development, besides, other organ tissue protection such as pancreatic as well as hepatic tissues are attributed to their reactive oxygen species scavenging along with inclining the level of the endogenous antioxidant enzymes in these organs <sup>[89, 90]</sup>. The flavonoids antioxidant activity is quietly associated with the hydroxyl groups number as well as position in the basic flavonoids scaffold, however, as much as the number of phenolic hydroxyl groups increase ( $\geq 3$  groups) the flavonoid's antioxidant influence enhances particularly in ring B. Meanwhile, declining these hydroxyl functionality by one slightly decline their antioxidant potential, yet, two hydroxyl functionality loss brings about considerable loss in their antioxidant activity on one hand. On the other hand, flavonoids glycosylation declines certain flavonols antioxidant influence as in case of quercetin, while, further aglycon modification with a second moiety further declines

this potential which is speculated to be due to the steric hindrance imposed by the added sugar motifs<sup>[91]</sup>.

Moreover, reports have demonstrated that plant phenolic and flavonoid secondary metabolites elicit hypolipidemic as well as hypocholesterolemic influences<sup>[92-96]</sup>. In this context, investigators have reported the advantageous antioxidant influences of flavonoids for hypercholesterolemia related injuries of oxidative stress<sup>[97]</sup>, particularly, fruits flavonoids that counteract hypercholesterolemia associated lipid peroxidation in animal model probably through promoting the antioxidant enzymes expression<sup>[78, 79]</sup>. Nevertheless, several flavonoids exhibit potent hypolipidemic influences<sup>[98, 99]</sup> that demonstrate a remarkably advantageous alteration in the pathogenic LDL/HDL ratio in clinical trials as they have declined the LDL level along with inclining the HDL level in patients with hypercholesterolemia probably through promoting disposition of cholesterol and triglycerides from the peripheral tissues to the catabolic and excretion tissues<sup>[100]</sup> explaining their reported hepato-protective influence<sup>[101]</sup>.

Regarding flavonoids anti-inflammatory influence, animal as well as preclinical studies have reported such effect<sup>[68]</sup>, however, flavonols is reported to be effective against both acute as well as chronic inflammations<sup>[102]</sup> through targeting the circulator inflammatory mediators TNF- $\alpha$  and IL-6<sup>[103]</sup>. In addition, flavonoids particularly their lipophilic aglycons can elicit lipoxygenase enzyme inhibitory influence<sup>[104, 105]</sup>, pectolarin for example is a potent 15-lipoxygenase enzyme inhibitor with of IC<sub>50</sub> 0.25 mM while Pectolarigenin exhibit moderate 46% inhibitory activity<sup>[106]</sup>. In *Nasturtium officinale*, the quantified rutin as well as phenolic phytochemicals have synergistically elicited anti-inflammatory influence<sup>[107, 108]</sup>. Rutin, anti-inflammatory influence is useful for various type of inflammation including cutaneous inflammations and contact allergic dermatitis<sup>[5, 107, 109-111]</sup> which is concentration dependent<sup>[107, 112]</sup> since rutin and other flavonoids can attenuate I $\kappa$ B protein degradation or phosphorylation indirectly besides, MIP-2 expression and MMP-9 activation down regulation in the lung tissues through Akt phosphorylation prohibition<sup>[113, 114]</sup>. Moreover, antithrombotic influence via platelet aggregation prevention is reported to flavonols<sup>[115]</sup>. However, the dimeric morelloflavone biflavonoid can inhibit snake venom phospholipase A2<sup>[116, 117]</sup> which is expected for the *Nymphoides indica* anti-snake bite counteracting influence of their leaf and roots extracts used internally as well as externally in Nicaragua, Sri Lanka<sup>[118]</sup>.

Concerning the reported plant flavonoids antimicrobial influences against various microbial pathogens particularly the parasitic ones<sup>[119, 159-162]</sup>, flavonoids from various plants particularly quercetin have been reported to exploit anti-leishmanial effect<sup>[119, 121-123]</sup>. In deed, (Tasdemir et al., 2006) have reported that the flavonoids fisetin, 3-hydroxyflavone, luteolin and quercetin exhibit anti-leishmanial influence with IC<sub>50</sub> values of 2.2, 2.9, 2.7, and 3.3  $\mu$ M, respectively<sup>[124]</sup>. Nevertheless, flavonoids particularly those from *Erythrina abyssinica* stem bark, are also reported to exploit antimalarial effect probably via inhibit the parasite's fatty acid biosynthesis (FAS II)<sup>[125]</sup>. In addition, *Nasturtium officinale* aqueous and alcoholic extracts antibacterial influence is attributed to their

flavonoids content<sup>[126]</sup>. In addition, flavonoids as well as their synthetic analogues are reported to be individually or synergistically exhibit powerful antifungal influences even against resistance strains<sup>[127, 128]</sup>. While, the geranylated flavonone, sophoraflavanone G and related flavonoid exploit vancomycin like promising antibacterial activity against methicillin resistant *Staph. aureus* with MIC of 7.3–14.7  $\mu$ M<sup>[129]</sup>. Interestingly, (Bettega, et al. 2016) believe that flavonoids from *Nasturtium officinale*, particularly rutin, express their antibacterial influence through declining the metalloproteinase of matrix-1 (MMP-1) gene expression as well as activity, besides the involvement of this mechanism in inclining the collagen formation/accumulation in wounds and ulcer areas explaining its wound healing effect<sup>[130]</sup> on one hand. On the other hand, other mechanisms are also proposed for flavonoids antimicrobial influence such as nucleic acid synthesis inhibitor, function interruption of cell membrane, interfering with energy production/metabolism<sup>[121]</sup>. Furthermore, flavonoids are known to exhibit antiviral influence since the middle of last century, however, the ring C, C3 hydroxyl group is critical for flavonols antiviral influence especially against type 1 herpes simplex virus, which make it much active than flavones<sup>[131, 132]</sup>. While, the flavonoid, baicalin is considered a promising anti-HIV candidate<sup>[133]</sup>, although, flavonoids from various plant extracts have been reported to exploit anti-HIV effect<sup>[134-140]</sup>.

Remarkably, the least prevalence rate of chronic/degenerative health conditions including tumors among the Mediterranean region population is significantly related to their high flavonoids/polyphenolics content plant diet<sup>[141]</sup>, since, the DNA oxidative injuries fundamentally correlated to mutagenesis, cancer, aging and other health anomalies<sup>[142]</sup>. The antioxidant as well as various critical intracellular signaling cascades/enzymes inhibitory influences may lies behind the dietary flavonoids cooked meat carcinogens counteracting influence<sup>[143]</sup>, however, their mode of action involve targeting various development stages of neoplasms, immune surveillance/response as well as immune system/cell components homeostasis<sup>[144, 145]</sup>. More than one flavonoids influences may contribute to their anticancer effect such as scavenging free radical, counteracting inflammation, as well as cytotoxic influences as in case of lutein<sup>[146-148]</sup>. In addition, other anticancer bioflavonoids exhibits their antineoplastic effect as well as other health related influences through targeting the gene related topoisomerase II enzymes<sup>[23, 24, 34-36]</sup> such as catechins<sup>[149, 150]</sup>. Interestingly, isoflavons/isoflavonones are reported to promote tumor cells apoptosis, while, flavonols like quercetin, kaempferol as well as epigallocatechin galates, besides, the flavonones like apigenin are reported to exploit their antineoplastic activity via cancer cells Ca<sup>2+</sup> channels functions modulation in different types of tumor cells<sup>[151]</sup>.

Furthermore, various plants phytochemical classes, flavonoids in particular such as 6-hydroxyflavonoides, flavonoids glycosides, isoorientin, kaempferitin, Isorhamnetin-3-O- $\beta$ -D-glucoside and other phenolic compounds have been reported to demonstrate antidiabetic influence via alpha-glucosidase or aldose reductase enzyme

inhibitory influences<sup>[106, 152-160]</sup> or even  $\alpha$ -amylase enzyme<sup>[161]</sup>.

However, liver glucokinase action promoting influence of flavonoids presumably via inclining the pancreatic islet insulin release<sup>[162]</sup>. In addition, flavonoids demonstrate antiglycation effect, particularly, the flavonol glycosides like isorhamnetin 3-robinobioside, hyperoside as well as isorhamnetin 3-galactoside-7-rhamnoside which exploit moderate antiglycation effect of IC<sub>50</sub> values of 48  $\mu$ M, 82  $\mu$ M and 155  $\mu$ M, respectively relative to the positive standard aminoguanidine (IC<sub>50</sub> 920  $\mu$ M)<sup>[163]</sup>. Silymarine for example, as a complex type flavonoid can reduce aging glycation end products in diabetic individuals via blocking specific advanced glycation end products receptors in both in vivo as well as in vivo studies<sup>[164]</sup>. As antiglycation compounds flavones are much potent than flavanones, isoflavones, and flavonols which is basically attributed to the structural requirements of such activity including C3, C5 and C7, C3', and C4' hydroxylation besides the impact of the hydroxyl groups methylation or glycosylation particularly in flavones, flavonones and flavonols<sup>[165]</sup>. It has been reported that (-)-epicatechin exhibits promotes the ATP-dependent pancreatic islets glucose stimulated insulin release in animal models besides a speculated enhancement of insulin biosynthesis along with cAMP phosphodiesterase enzyme inhibition<sup>[166]</sup> besides, inducing the peripheral AMP dependent protein kinase in skeletal muscles as well as white adipose tissues. Furthermore, it has been demonstrated that flavonoids prohibits intestinal glucose transporters activity hence, inclines peripheral glucose consumption<sup>[167, 168]</sup> on one hand. On other hand, flavonoids such as quercetin, and kaempferol inclines the pancreatic islets number as well as hexokinase glucokinase action in animal model<sup>[168]</sup>. In addition, plants polyphenols exploit pancreatic lipase inhibitory effect in rat models<sup>[169, 170]</sup>. Finally, the plant flavonoids and their analogues are reported to be type 2 aldose reductase (ALR2) inhibitors, hence counteracting the diabetes mellitus complications<sup>[171, 172]</sup>.

### Some Specific Quercetin Biological Influences:

As one of the fundamental dietary flavonoids distributed in various plant parts leaves, seeds, fruits and flowers like in watercress<sup>[61, 173]</sup>, Quercetin is presumed to constitute 50% of the flavonoids content, however, its level is plant species/varieties type and cultivation/processing conditions, although its level abundance in red onion not exceed 200–600 mg/kg<sup>[174]</sup>. As a raw material, Quercetin aglycon is yellow color powder lipophilic substance freely soluble in alcohols and lipids, poorly soluble in hot water while insoluble in cold water. Quercetin beside being a well known antioxidant substance, it exhibit various biological influence such as neurodegenerative diseases counteraction, antimicrobial, antiviral, anticancer, anti-inflammatory, antidiabetic, cardiovascular protection,, hepatic protection, immune modulator, antiviral, as well as aldose reductase inhibitory influences<sup>[131, 173, 175-177]</sup>. In addition, it synergistically enhances the antineoplastic activity of chemotherapeutic agent of multiple drug resistance<sup>[175, 176]</sup>. The biosynthesis of Quercetin involve the condensation of three malonyl CoA and one p-coumaroyl CoA molecules via chalcone synthase enzyme activity into naringenin-chalcone which is cyclized via action of chalcone isomerase enzyme

into the first flavonoid in the biosynthetic pathway, naringenin that is hydroxylized at the ring C, C3 carbon into dihydrokaempferol, that is oxidized at C2 and C3 carbon into  $\Delta$  2,3 double bond flavonol compound, kaempferol. The later flavonol is converted into dihydroquercetin by mean of flavonol 3-hydroxylase enzyme then into quercetin by action of flavonol synthase enzyme<sup>[178]</sup>. Chemically, quercetin possess biological influences determining five hydroxyl functionalities, besides, the existence of two sub-classes of derivatives, the O-glycosides and ethers regardless some minor sulfate or prenyl substituted derivatives<sup>[111]</sup>. Glycosylation of quercetin lipophilic aglycone occur at one of its C3 or C7 hydroxyl groups that may contains alkylation at other positions that may reaches to five ether alkylations<sup>[179]</sup>. In general, most of Quercetin biological influences regarding counteracting/protection of many oxidative stress based human health anomalies such as cancer, atherosclerosis and inflammatory condition fundamentally relies on its antioxidant as well as anti-inflammatory effects. Quercetin also exploits its antioxidant influence via inducing the endogenous antioxidant enzymes to neutralize at least thirty type of oxidative carcinogens<sup>[180-182]</sup>.

Interestingly, quercetin/its derivatives (Quercetin-3-O- $\beta$ -d-glucopyranoside) through their antioxidant influence counteract hydrogen peroxides attributed cytotoxicity hence decreasing the generation of reactive oxygen species<sup>[206]</sup>. Like myricetin, Quercetin is reported to be in vitro counteract the, human lymphocytes, hydrogen peroxide-induced DNA damage<sup>[183]</sup> besides imposing significant decline in colon cancer cell lines<sup>[184-186]</sup>. The antioxidant influence particularly against LDL lipid peroxidation is attributed to its free radicals scavenging as well as trans metals chelating potentials which is believed to be strongly associated with structural features of the Quercetin basic scaffold. Dihydroxylation on ring B as well as unsaturation of ring C, at C2 and C3 along with 4-oxo functionalities are the basic determinants of its antioxidant activity<sup>[180-182]</sup>. Quercetin has antineoplastic effect against diverse types of tumors including; ovarian cancer<sup>[187, 188]</sup>, melan-a melanocyte cells melanogenesis<sup>[189]</sup>, human breast cancer MCF-7 cells through cell cycle regulation via targeting mitochondrial caspase cascade promotion as well as attenuation of tumor cells adhesion/metastasis<sup>[190-192]</sup>. In fact, Quercetin anticancer activity against breast cancer is maintained via miRNA expression regulation, hence, enhancing expression of the pro-apoptotic-Bax (Bcl-2 associated X) and caspase-3 along with declining the expression of oncogenic-EGFR through inkling the expression of miR-146a that bring about tumor cells apoptosis besides, blocking tissues invasion by the tumors cells as in vitro demonstrated in breast cancer cell lines MCF-7 and MDA-MB-231 models<sup>[193]</sup>. Quercetin also exhibits anticancer activity against colon tumors, hence, declining cancer growth, cancer cells survival/proliferation rate suppression, apoptosis/autophagy induction, and cell cycles arresting via targeting various molecular targets such as MYC, B-cell lymphoma (Bcl)-2, Bcl-xl expression depression along with p53, caspase-3, -9, cleaved Poly (ADPribose) polymerase (c-PARP) expression promotion in CRC cells<sup>[194-197]</sup>, besides, mitochondrial membrane potential reduction<sup>[198-200]</sup>. In this context, Quercetin provokes the p38MAPK gene that stimulates caspase-3

along with PARP protein in the colon cancer DLD-1 cells<sup>[201]</sup>, while, promotes apoptosis in HT-29 and HCT-116 colon cancer cell lines via rapamycin (AMPK/mTOR)<sup>[202]</sup> in addition to AMPK/p38<sup>[203]</sup> pathways targets modulation that provokes the expression of sirtuin 2in a p53-independent manner along with inducing the generation of reactive oxygen species intracellularly<sup>[200, 204]</sup>. Remarkably, Quercetin is reported to attenuate the colon cancer cells CT26 metastasis via epithelial mesenchymal transition (EMT) through N-cadherin,  $\beta$ -catenin, and snail expression attenuation along with inclining the E-cadherin expression<sup>[194]</sup>, besides, reported anti-invasive as well as anti-migration influence in HT-29, CT26 and Caco-2 cells via declining their migration ability by mean of MMP-2 and MMP-9 expression prohibition<sup>[194, 195, 205]</sup>. In addition, in murine model, Quercetin have been reported to decline the lung neoplastic masses due to colorectal-lung metastasis at a dose of 10 or 50 mg/kg via inclining p-Erk, p-JNK and pp38MAPK, whereas, declining MMP-2, MMP-9, N-cadherin,  $\beta$ -catenin, Snail, E-cadherin expressions. However, in vitro cytotoxic influence on CT-26 through inclining c-PARP, caspase-3,-9 while declining Bcl-2 and Bcl-xL expressions leading induce apoptosis<sup>[194]</sup>. However, quercetin can also counteract colorectal carcinomas in clinical trials<sup>[206]</sup>. Meanwhile, quercetin/isoquercetin formulation (CAT IQ) is recently reported to be in phase 2 and phase 3 clinical trials for colorectal cancer adjuvant therapy<sup>[207]</sup>. In vitro investigation of Quercetin at 25-200  $\mu$ M concentration for 48 h, induce apoptosis via declining p-Akt, MYC expression along with cell proliferation inhibition at G0/G1 phase as well as arresting cell cycle through declining Bcl-2 while inclining Bax, p53, caspase-3 expression in HT-29<sup>[196]</sup>. In other study, in vitro study Quercetin at concentration of 25-100  $\mu$ M for 24 h provokes apoptosis in Caco-2 and SW-620 cell lines via inclining Bax and caspase-3,-9, whereas, declining Bcl-2 and NF- $\kappa$ B expressions<sup>[197]</sup>. In a third in vitro study, the administration of Quercetin at concentration 5-50  $\mu$ M for 24-72 h in provokes apoptosis in colon DLD-1 cancer cell line via declining MMP<sup>[198]</sup>. In a fourth in vitro study, the administration at concentration of 25-100  $\mu$ M for 6-24h provokes apoptosis in HCT-116 via increasing reactive oxygen species generation besides inclining the SIRT-2 and p-AMPK/pp38MAPK expressions, while, declining MMP and p-mTOR expressions<sup>[200, 202]</sup>. In a fifth in vitro study, the administration of Quercetin at concentration of 50  $\mu$ M for 48h provokes apoptosis and inhibits cell proliferation in Caco-2 and colon cancer DLD-1 cell lines via inclining JNK and c-Jun expressions while, declining CBI receptor, Wnt/ $\beta$ -catenin, p-GSK3 $\beta$ , p-PI3K/Akt, p-S6, p-4EBPI and p-STAT3 expressions<sup>[195]</sup>. In addition, Quercetin/ its derivatives have been reported to induce apoptosis at concentrations of 25-100  $\mu$ M for 24h in HCT-116 cell line via inducing AMPK and HIF-1 expressions as well as reducing hypoxia, whereas, cell cycle arrest in tumors particularly at G0/G1 phase, as reported by (Yang et al., 2016)<sup>[196]</sup>, at 50 mg/kg dose for 24 days in HCT-116 Xenograft model<sup>[208]</sup>. However, G2/M phase arrest is also reported in HT-29 and HCT-116 for Quercetin 5-40  $\mu$ M for 24h through inducing oxidative stress, autophagy with increasing LC-I/II, SQSTM1/p62, p-Akt/PI3K, p-Erk1/2, p-JNK, and p-p38MAPK, while, declining Beclin expressions

<sup>[209, 210]</sup>. In other study, (Hashemzaei et al., 2017) have reported that Quercetin at concentration of 10-120  $\mu$ M for 48h, induces apoptosis in CT-29, while, decreasing the tumor volume in an in vivo CT-26 Xenograft model<sup>[211]</sup> hence, enhancing the survival rate. Furthermore, Quercetin is also reported to potentiate the antineoplastic influences of other phytochemicals for example in HT-29 cells resveratrol-quercetin combination can prohibit the specificity protein (Sp) transcription factors Sp1, Sp3, and Sp4 expression along with Sp-dependent survivin gene (anti-apoptotic gene)<sup>[212]</sup>. In another case, Quercetin has been reported to enhance the antineoplastic potential of isorhamnetin via elevating their blood level<sup>[174]</sup>. A third case of curcumin-quercetin combination therapy (in a dose of 1.44 g curcumin and 60 mg quercetin /day for 6 months) have been reported to decline the adenomas in familial adenomatous polyposis size as well as number<sup>[213]</sup>. A fourth case involve the use of 500  $\mu$ M (quercetin + rutin) to reduce reactive oxygen species in patients with colon cancer<sup>[214]</sup>. Quercetin is reported to ameliorate GST and CYP1A1 activities<sup>[215]</sup>, besides, being inhibitor to ATPase of the mitochondrial soluble and particulate forms of the enzyme at low concentration despite being un effective on sub-mitochondrial particles oxidative phosphorylation process<sup>[216]</sup>, hence, attenuates energy production process. However, quercetin through its antioxidant influence besides attenuating the apoptotic along with promoting the growth factors, it protect the testes Sertoli cells<sup>[217, 218]</sup> as what is encountered with other flavonoids apigenin and kaempferol<sup>[219, 220]</sup>.

Furthermore, Quercetin have been demonstrated to exploit anti-inflammatory influence via toll like receptor4 (TLR4), NF- $\kappa$ B, MMP-2 and MMP-9 genes along with inflammatory mediators expressions whereas, inclining E cadherin expression in Caco-2 cells at 5  $\mu$ M concentration<sup>[205]</sup>. While, others have reported NF- $\kappa$ B p65 nuclear translocation modulatory influence in changes in human polymorph nuclear cells via modulating the signaling TLR-NF- $\kappa$ B pathway<sup>[221]</sup>. However, through COX-2 dependent reactive oxygen species development as well as p-Akt and p-GSK-3 $\beta$  expression attenuation, quercetin suppresses HT-29 and HCT-15 cells survival rates at 20-100  $\mu$ M concentration for 24h, hence, inhibiting cell proliferation, besides, Inducing apoptosis<sup>[222]</sup>. In addition, it is reported that Quercetin effects the expression of the reactive oxygen species-sensitive nuclear transcription factors, pro-inflammatory cytokines, and adhesion molecules in the smooth muscle and endothelial cells of the human aorta<sup>[223]</sup>, while others have attributed the usefulness of quercetin, kaempferol, kaempferol methyl ether, and other phytochemicals containing plants against snakebites for these flavonoids anti-inflammatory characteristic<sup>[224-228]</sup>. The quercetin pharmacokinetics of 60-2000 mg/m<sup>2</sup> body surface area dose have revealed its safety at a dose of (945mg/m<sup>2</sup>), distribution volume of (3.7L/m<sup>2</sup>), distribution  $t_{1/2}$  of 0.7-7.8 min, elimination  $t_{1/2}$  of 3.8-86 min. while, toxicity adverse effects includes hypertension, emesis, nephrotoxicity, and hypokalemia<sup>[229]</sup>. However, at a dose of 200 mg others have reported  $C_{max}$  of  $2.3 \pm 1.5$   $\mu$ g/mL, while,  $T_{max}$  of  $0.7 \pm 0.3$ h<sup>[230]</sup>. Several nano-formulations have been reported for enhancing quercetin bioavailability in animal models such as curcumin-quercetin nano-capsules to potentiate their

anticancer activity against breast neoplasms<sup>[231]</sup>, besides, quercetin-doxorubicin nano-capsules to enhance doxorubicin anticancer activity against resistant MCF-7 cell line in vivo<sup>[232]</sup>. However, it is necessary to note that quercetin, luteoline, kaempferol and some other flavonoids process peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) antagonism<sup>[233]</sup>.

Moreover, the flavonoids such as Quercetin and myricetin antidiabetic and its complications counteracting influences is thoroughly reported<sup>[234, 235]</sup> via various mechanism including; first inhibition of protein tyrosine kinase critical for the insulin post receptor binding<sup>[157, 236]</sup> which may explain *Nymphoides oristatum* antidiabetic effect<sup>[157]</sup>, second; potent inhibition of proteins (like albumin) glycation<sup>[237]</sup>, third; reducing intestinal absorption of glucose<sup>[238, 239]</sup>. However, regarding quercetin activity against diabetes complications, it is reported that quercetin rich ethyl acetate fraction of *Rhododendron mucronulatum* has exploited aldose reductase inhibitory activity with IC<sub>50</sub> of 2.11 $\mu$ M<sup>[240]</sup>. Meanwhile, Quercetin exhibits 635 and 73% declining influence against lens aldose reductase enzyme in healthy as well as diabetic rat models<sup>[235]</sup>, while, it has exploited 50% inhibition of human lens aldose reductase enzyme at concentration of 5 x 10<sup>-6</sup> M although other flavonoids also has possessed such inhibitory effect<sup>[241]</sup>. In fact, it is reported that quercetin acts as a non-competitive inhibitor of lens aldose reductase enzyme by 95% and 80% at 10<sup>-5</sup> M and 10<sup>-4</sup> M concentrations<sup>[242]</sup>.

Remarkably, quercetin, quercitrin and luteolin containing plants have been reported to demonstrate antiemetic drugs mimetic influence on the vomiting center<sup>[118]</sup>, besides,  $\alpha$ 1 $\beta$ 1 $\gamma$ 2s GABAA receptors agonistic influence mediated anxiolytic effect<sup>[243]</sup>. In addition, quercetin have been reported to exhibit PDE5 enzyme inhibitory influence explaining its therapeutic benefits in cases of cardiovascular diseases, stroke, pulmonary hypertension, female sexual dysfunction, premature ejaculation, leukemia, as well as renal failure<sup>[244]</sup>, besides, the potential involvement of quercetin/3-methoxyquercetin acetylcholinesterase enzyme inhibitory effect<sup>[245]</sup>. Quercetin also has been reported to exploit type 1 isozyme of 5 $\alpha$ -aldose reductase enzyme, however, other flavonols like kaempferol inhibits the isotype 2 of this enzyme despite a solely single hydroxyl group difference between the two flavonols<sup>[246]</sup>.

### Najas And Nuphar Aquatic Plants Species Polyphenolic And Flavonoids Contents:

Aquatic plants that is detected in Iraqi marsh lands are thoroughly investigated for their polyphenolic, flavonoids and other phytochemicals for their classes, level as well as total class/individual metabolite content. Watercress, *Nasturtium officinale* for example its hepato-protective influence is attributed to its enrichment of flavonoid (flavonols) as well as phenolic phytochemicals<sup>[247]</sup>. In addition, the flavonoids, phenolics and tannins richer ethyl acetate extract exhibits extremely much potent antibacterial activity against *Staphylococcus aureus* PMFKGB12 and *Bacillus subtilis* at MIC < 78.13  $\mu$ g/mL as long as *Escherichia coli* ATCC25922 BIC<sub>50</sub> at 719  $\mu$ g/mL as

compared to water extract which is apparently inactive. The total phenolic, flavonoids and tannin contents of water extract of *Najas minor* is 2.46  $\pm$  0.11 mg gallic acid/gm extract, 1.25  $\pm$  0.03 mg rutin/gm extract and 0.1  $\pm$  0.09 mg catechin/gm extract respectively. However, the total phenolic, flavonoids and tannin contents of ethyl acetate extract of *Najar minor* is 20.58  $\pm$  0.11 mg gallic acid/gm extract, 89.72  $\pm$  0.61 mg rutin/gm extract and 1.93  $\pm$  1.83 mg catechin/gm extract respectively<sup>[248]</sup>, although individual flavonoid type metabolites have not been reported so far to our knowledge. However, *Nuphar lutea* commonly known as yellow lily, mature leaves have been reported to exploit high levels of phenolic phytochemicals particularly the polyphenolic metabolites that contribute to the leave's extract fungistatic potential, besides, other phytochemicals related to health beneficial biological effects<sup>[249]</sup>. Nevertheless, shading declines the biosynthetic extent of the polyphenolic phytochemicals due to the attenuation primary biosynthetic pathway enzyme phenylalanine ammonia-lyase (PAL) which is light dependent<sup>[250]</sup>. In this context, the plant leaves phenolic phytochemicals is enhanced with increasing light intensity leading to the incline of the phenolic content from 31% to 72%, however, the water/soil nitrogen content inversely proportional to the biosynthesis of phenolic compounds where the reduction of nitrogen level from 25% to 15% inclines the phenolic compound content from 88% to 225% in the leaves<sup>[251]</sup>.

Furthermore, phenolic acids such as caffeic, ferulic, and 3,4-dimethoxy-cinnamic acids besides, flavonols and flavonones are reported for *Nuphar variegatum*<sup>[252, 253]</sup>, although chalcones and flavonols derivatives are speculate to exist in the plant seedling exudate due to the detected high level of variously substituted anthocyanidin diglycosides<sup>[254]</sup>. In this context, 0.2 $\mu$ g/mg dry weight of phenolic compounds including phenolic acids and 1.3  $\mu$ g/mg dry weight of tannins, hydrolysable tannin and gallotannin have been reported to exist in the seedling exudate of *Nuphar leuta*<sup>[255]</sup>. In addition, a complex collection of hydrolyzable tannins are isolated from *Nuphar variegatum* roots contributing to the plant's extract antibacterial activity<sup>[256]</sup>, however, ellagic acid is also detected in the leaves of *Nuphar lutea* (L.) Sm.<sup>[257]</sup>, however, complex mixture of polymeric ellagotannins and gallotannins from *Nuphar japonicum* DC and *Nuphar variegatum*<sup>[258-261]</sup>, although individual flavonoid type metabolites have not been reported so far to our knowledge.

### Nymphoides Aquatic Plants Species Polyphenolic And Flavonoids Contents:

Nymphoides are commonly known as floatingheart is a third type of aquatic plant, however its various species have been reported to possess broad array of phytochemicals including polyphenolic phytochemicals such as flavonoids like methylquercetin, tannins and phenolic acids like ferulic acid<sup>[262]</sup>. These phytochemicals are mostly lipophilic compounds particularly the phenolic acids and flavonoids aglycones<sup>[262-264]</sup>. The phenolic as well as flavonoids content is summarized in table (1). The Nymphoides genus plants (like *N. hydrophylla*, *N. indica* and *N. macrospermum*) are reported to possess various classes of phytochemicals

including phenolic compounds like polyphenolics compounds including phenolic acids, flavonoids and coumarin, in addition, triterpenes, carbohydrates and glycosides. Among the characteristic phytochemicals of this genus are methyl quercetin and ferulic acid<sup>[262, 265]</sup>. In addition, flavonoids are detected in *N. indica*<sup>[266]</sup>, however, always medium polarity solvents/isolated fraction such as alcohols, chloroform and ethyl acetate are rich in flavonoids as well as terpenes<sup>[263]</sup>. (Amin A. 2016) has reported that the total phenolic compounds and flavonoids in *Nymphoides indica* that explain the greatest total phenolic as well as flavonoids contents contributing to the crude extracts, methanolic and acid acetate fractions, although both have exhibited moderate antioxidant effects with IC<sub>50</sub> value of 81 µg/ml for ethyl acetate fraction followed by 97 µg/ml methanolic fraction followed by 119 µg/ml for chloroform fraction although methanolic fraction has exploited better antiglycation influence, yet, has speculated very low- low total phenolic compounds and flavonoids<sup>[106]</sup> as what (Dudonne, et al. 2009) have reported<sup>[267]</sup>. Nevertheless, (Amin, et al. 2016), has supposed another non-phenolic plant metabolites also contributing to the extracts antiglycation influences, but they concluded that phenolic compounds, particularly, the flavonoids are the major contributors to the plant antiglycation influence particularly the ethyl acetate extract via their antioxidant potential as well as its moderate antidiabetic influence due to its  $\alpha$ -glucosidase inhibitory effect<sup>[263]</sup>. In addition, the n-butanol fraction exhibits 24% antiglycation activity attributed to its flavonoids and monoterpenes content<sup>[106]</sup>. Nevertheless, plant leaves extracts (particularly ethyl acetate) exhibits moderate antiglycation effect weaker than quercetin while, mild-moderate  $\alpha$ -glucosidase inhibitory influence owed to the extract's phenolic acids as well as flavonoids content although, the encountered elevated antioxidant influence is also reported to their high content. In fact, the order of antioxidant influence of *Nymphoides indica* leaves extracts are in the following order; ethyl acetate extract with IC<sub>50</sub> value of 81 µg/mL > methanolic extract with IC<sub>50</sub> value of

97 µg/mL > chloroform extract with IC<sub>50</sub> value of 115 µg/mL<sup>[263]</sup>. Moreover, *N. indica* extracts have been reported to exhibit antiprotozoal influence of moderate IC<sub>50</sub>. In this context, the plant methanolic fraction is attributed to its flavonoids and coumarins content that are synergistically confer the plant's antimicrobial effect<sup>[106]</sup>. Recently, (Hanif, et al., 2022) have reported various antioxidant influences of the different *N. Indica* rhizome extract fraction in different in vitro antioxidant assays. For example, in DPPH assay the methanolic fraction and chloroform fractions exhibit potent antioxidant influence at IC<sub>50</sub> value of 40.3±0.04 µg/mL and 40.05±0.21 µg/mL respectively, while, in FRAP assay the methanolic fraction, chloroform and ethyl acetate fractions possess potent antioxidant influence at IC<sub>50</sub> value of 756.2±0.06 µg/mL, 225.0±0.04 µg/mL and 193.0±0.21 µg/mL respectively. However, the *N. Indica* rhizome extract fractions, significant antimicrobial influence against *Klebsiella pneumoniae* is reported for chloroform fraction followed by methanolic fraction with MIC values of <0.156mg/ml and 0.625mg/ml respectively, while, the fractions anti-biofilm forming effect is demonstrated to the chloroform as well as ethyl acetate fractions at IC<sub>50</sub> values of 1.73 mg/ml and 1.76 mg/ml respectively. However, the reported antioxidant, antimicrobial and antibiofilm influences of the extract's fractions are owed to their flavonoids content<sup>[268]</sup>. However, phenolic phytochemicals existed in the crude methanolic *Nymphoides hydrophylla* leaves extracts has been reported to be significantly correlated to its mild anthelmintic, moderate antioxidant and potent cytotoxic effects<sup>[265]</sup>. Earlier (Amin, et al., 2014) have reported that the order of *Nymphoides indica* leaves extract fractions antioxidant activity is ethyl acetate >90% methanol > chloroform with IC<sub>50</sub> values of 147 µg/mL, 211 µg/mL, and 380 µg/mL respectively. However, the plant leaves extract fractions antiglycation influence is in the following order n-butanol > chloroform > ethyl acetate >90% methanol fraction with IC<sub>50</sub> values of 32 µg/mL, 64 µg/mL, 69 µg/mL, and 86 µg/mL respectively<sup>[269]</sup>.

**Table 1:** Reported total phenolic compounds and flavonoids in *Nymphoides* species:

<b>Nymphoides specie</b>	<b>Part used</b>	<b>Type of extract</b>	<b>Total phenolic content</b>	<b>Total flavonoids content</b>	<b>Ref.</b>
<i>Nymphoides indica</i>	Leaves	crude extract	28.88 mg of GAE/g	70.28 mg RUE/g	[106, 263]
<i>Nymphoides indica</i>	Leaves	90% methanolic fraction	31.87 ± 0.83 mg GAE/g	62.34 ± 0.9 mg RUE/g	[106, 263]
<i>Nymphoides indica</i>	Leaves	Chloroform fraction	9.76 ± 0.96 mg GAE/g	17.52 ± 1.22 mg RUE/g	[106, 263]
<i>Nymphoides indica</i>	Leaves	Ethyl acetate fraction	43.1 ± 0.54 mg GAE/g	73.44 ± 1.23 mg RUE/g	[106, 263]
<i>Nymphoides indica</i>	Leaves	n-butanol extract	16.38 ± 1.07 mg GAE/g	10.57 ± 0.39 mg RUE/g	[106, 263]
<i>Nymphoides hydrophylla</i>	Roots and rhizomes	Aqueous extract	1.110 ± 0.318 mg GAE/g	-----	[264]
<i>Nymphoides hydrophylla</i>	Roots and rhizomes	Alcoholic extract	1.800 ± 0.350 mg GAE/g	-----	[264]
<i>Nymphoides hydrophylla</i>	Leaves	Crud methanolic extract	12.5 ± 0.167 mg GAE/gm	-----	[265]
<i>Nymphoides hydrophylla</i>	Whole plant	Aqueous extract	48.83 mg GAE/g	6.86 mg QE/g	[270]
<i>Nymphoides hydrophylla</i>	Whole plant	Ethanol extract	79.43 mg GAE/g	197.21 mg QE/g	[270]
<i>Nymphoides cristata</i> (Roxb.) O. Kuntze	Leaves	acidified methanol/ acid hydrolyzate	3.82 ± 1.02 mg GAE/g DW	23.28 ± 0.54 mg QE/g DW <b>Flavonols:</b> 6.71 ± 0.44 mg QE/g DW	[271]

\* GAE: gallic acid equivalent., \*\* RUT: rutin equivalent., \*\*\* GE: quercetin equivalent., \*\*\*\* DW : dry weight.

*Nymphoides indica* (L.) Kuntze leaves alcoholic extract has been reported to contain various phytochemical classes including Polyphenolic component such as Flavonoids like Methyl quercetin, besides, phenolic acids like Ferulic acid<sup>[263]</sup>, besides, . However, the decomposition of dry materials *Nymphoides indica* in water leads to the liberation of polyphenolic compounds to water<sup>[272]</sup>. In addition it is reported that the polyphenolic as well as flavonoids content in the ethanolic extract is greater than that in the aqueous extract explaining its greater antioxidant influence, yet, according to the HPLC analysis the superior content of flavonoids (2.8 times ) particularly quercetin and kaempferol in addition the polyphenolic content (1.6 times) in the ethanolic extract as compared to the aqueous extract explains the reported antioxidant effect. Thus, the magnitude of the antioxidant influence is attributed to the quantity and quality of the polyphenolic compounds in particular kaempferol and quercetin<sup>[270]</sup>.

Interestingly, some aqueous extracts from thia/Lanna herbal recipe from MANOSROI II database included *Nymphoides indica* L. have revealed a considerable correlation between the phytochemical contents including flavonoids as well as tannins and the observed anti-proliferative, the MMP-2 inhibitory and metal chelating inhibitory influences in all studied extracts<sup>[273]</sup>. However, more than 40% prohibition of the MMP-1 mRNA expression have been reported for the *N. peltata* extract butanolic fraction at 10 µg/mL concentration, thus anti-aging beneficial use of *N. peltata* nominate it for cosmetics formulations<sup>[274]</sup>. Furthermore, (Madhavan, et al., 2011) has reported the existence of phenolic compounds as well as tannins in acetone, ethanol and aqueous rhizome as well as roots extracts of *Nymphoides indica* (L.) Ktze., whereas, flavonoids in ethanol and aqueous extracts<sup>[275]</sup>. However, (Hanif, et al., 2021) have reported the significant correlation between the moderate antioxidant, α-glucosidase inhibitory and antiglycation influences of these (aqueous and alcoholic extracts) as well as other non polar extracts of to the *Nymphoides Indica* rhizome to their flavonoids and terpenes content<sup>[263, 276]</sup>, besides, its reported anticonvulsant effect<sup>[277]</sup>. In addition, *Nymphoides hydrophylla* roots as well as rhizome extracts also exhibits similar phytochemical profile of phenolic compounds and tannins in the ethanolic and aqueous extracts, along with coumarins in the ethanolic extract, while, phenolic compounds, tannins and flavonoids in the acetone extract. Nevertheless, the total polyphenolic compounds explains the moderate antioxidant influence of the *N. hydrophylla* aqueous and alcoholic extracts<sup>[264]</sup>. It is reported that anti-HIV antiviral utilization is specified for whole plant crude extract of *Nymphoides peltata* (S.G. Gmel.) Kuntze<sup>[278]</sup>. Furthermore, it is also reported that *Nymphoides indica* purely isolated flavonoids exploits antipyretic, analgesic, antirheumatism, and anticabies<sup>[279]</sup>, however, those isolated from *Nymphoides hydrophylla* Leaves and seeds have been reported to elicit antipyretic, antiulcer, anti-snake-bite, anti-scorpion sting, anti-insect bites anti-juandice effects<sup>[280]</sup>. However, earlier (Amine, et al., 2014) have reported the isolation of four flavonoids from various 90% methanolic, chloroform, ethyl acetate, and butanol *Nymphoides indica* leaves extracts. The methanolic extract has exhibited antimicrobial (antifungal and antibacterial) as well as cytotoxic influences at IC<sub>50</sub> values

of 32 µg/mL and 38.9 µg/mL respectively, besides, n-hexane extract has exhibited antibacterial as well as antifungal with IC<sub>50</sub> of 19.15 µg/mL<sup>[269]</sup>.

Two Quercetin glucose glycosides derivatives are obtained from *Nymphoides indica* crude extract fractions; methanol, ethyl acetate and *n*-butanol fractions which are Quercetin 4'-O-glycoside which is the dominant flavonoid and 7-O-glycoside, besides, one methylated Quercetin aglycone<sup>[106, 264, 266]</sup>. In addition, these flavonoids glycosides also exhibit antiglycation influence in the follow order 3-O-Methylquercetin-7-O-β-glucoside with inhibition percentage of 54% at 0.67 mM with IC<sub>50</sub> value of 0.42 mM > 3,7-Di-O-methylquercetin-4'-O-β-glucoside with inhibition percentage of 44% > 3,7-di-O-methylquercetin with inhibition percentage of 39%. Furthermore, the isolated flavonoids exploit mild-moderate α-glucosidase prohibition influence as compared to standard flavonoids, Quercetin, although 3-O-Methylquercetin-7-O-β-glucoside is devoid of this activity. The flavonoid, 3,7-Di-O-methylquercetin-4'-O-β-glucoside exhibit 45% enzyme inhibitory influence, while, 3,7-di-O-methylquercetin exhibits 27% enzyme inhibitory influence. The flavonoid, 3,7-Di-O-methylquercetin-4'-O-β-glucoside have found to exhibit weak antiparasitic influence against *Trypanosoma brucei*, *Trypanosoma cruzi*, and *Leishmania infantum* with IC<sub>50</sub> values of 8.4 µM, 30.0 µM and 32.5 µM respectively<sup>[106, 263]</sup>. Nevertheless, two flavonoids isolated from *Nymphoides indica* rhizomes extract 3,7-di-O-methylquercetin-4'-O-β-glucoside has been reported to exploit anti-aging influence at > 5 µg/mL concentration, although fifteen flavonoids was previously isolated from the aerial parts of the plant. However, 3-O-mono-, 3-O-diglycosides, 4'-O-glucosides are characteristic to four *Nymphoides* species<sup>[281]</sup>. The flavonoid, quercetin 3,7-dimethyl ether 4'-glucoside has been reported to exploit anti-inflammatory influence via dose dependent blocking cytokines (such as TNF-α, IL-1, IL-6, and IL-8), COX-2 protein, and chemokines expressions produced by keratinocytes at concentration at a dose of 10 µg/mL, besides, prohibition of the expression of skin barrier peptide along with inhibition of hyaluronic acid synthesis<sup>[282]</sup>. The reported *Nymphoides* species isolated flavonoids in different parts various extraction solvents are listed in table (2). Moreover, whole plant aqueous as well as alcoholic extracts of *Nymphoides hydrophylla* in Taiwan have demonstrated the existence of polyphenolic compounds particularly phenolic acids like gallic as well as ellagic acid in addition to flavonoids such as quercetins and kaempferols<sup>[282]</sup>.

Finally, a very early work by (Bohm, et al, 1986) have revealed that Menyanthaceae family to which the genus *nymphoides* characterized by biosynthesis of some flavonoids pattern based on Quercetin, kaempferol, quercetin/kaempferol methylated derivatives and their glycosides. Five various aglycones are identified in the nine species including simple kaempferol, isorhamnetin, and quercetin, besides, their O-methyl derivatives are identified in all species of *Nymphoides* particularly quercetin aglycone. Some species of *Nymphoides* have possessed simple flavonoids pattern including quercetin alone as in case of *N.exigua* and *N. peltata*, besides, kaempferol and quercetin combination as in case of (*N. cordata*, *N. crenata*, and *N. cristata*, however, O-methylation mostly happens at

C3, C7 and C3' hydroxyl groups. In the nine studied species, isorhamnetin, 7-O-methylquercetin, 7-O-methylkaempferol, 3,7-di-O-methylquercetin, and 7,3'-di-O-methylquercetin are detected in *Nymphoides* species, yet, Isorhamnetin, 7-O-methylquercetin, and 3,7-di-O-methylquercetin as well as 3-O-methylquercetin is identified in two species *Nymphoides geminate* and *Nymphoides indica*, yet, 7,3'-di-O-methylquercetin is characteristic to *N. geminata* exclusively indicating an elevated degree of O-methylation. Nevertheless, a trace amount of dihydroflavonol in *Nymphoides grayana*. In addition, isorhamnetin and 3,7-di-O-methylquercetin are identified in *N. fallax* as well as *N. grayana*, whereas, 7-O-methylquercetin is identified in four species *N. indica*, *N. fallax*, *N. grayana*, and *N. geminate* that produce simple as well as several types of O-methylated quercetin and/or kaempferol aglycones. Five species of *Nymphoides* fails to biosynthesize O-methylated flavonols including *N. peltata*, *N. cordata*, *N. crenata*, *N. cristata*, and *N. exgua* thus produce only quercetin and/or kaempferol aglycones. furthermore, some species are identical in their identified flavonoids aglycone profile as incase of as in case of *N. grayana*, and *N. fallax*, although, *N. grayana* characterized by C3' O-methylation, however, it varies from either of *N. fallax* or *N. indica* by its more complex glycosides derivatives. In this context, the three Australian species, *N. crenata*, *N. exgua*, and *N. geminata* varies from each other

in both flavonoids aglycones and glycosides pattern [283]. Moreover, flavonoids O-glycosylation may occur at single position at C3 position, and double O-glycosylation at C3 and C4' positions of kaempferol, quercetin and isorhamnetin which are identified at two *Nymphoides* species including *N. geminate* and *N. indica*. In addition. The 3,7-di-O-methylquercetin-4'-O-glucoside is identified in four species including *N. indica*, *N. grayana*, and *N. geminate*. In addition, despite both of *N. fallax* and *N. grayana* are distinguished from each other by the presence of quercetin 3-O-galactoside in *N. grayana*. Remarkably, 4'-O-glucosides mostly occur in 3,7-di-O-methylquercetin are detected in four *Nymphoides* species including *N. indica*, *N. fallax*, *N. grayana*, and *N. geminate*, while, 3-O-glucosides are encountered with other five species making this pattern of flavonoids glycosylation is the common one. In addition, *N. fallax* varies from *N. indica* by glucosides acylation as well as monorhamnosides are identified in the first specie. Some flavonoids 3-O-diglycosides derivative are encountered, however, some occur of the same sugar as the inner residue while arabinose and rhamnose occur is the outer residue. Similarly, glucose as well as rhamnose quercetin 3-O-triglycoside is identified in *N. cordata* [283]. The flavonoids aglycones and glycosides derivatives is listed in table (3) modified from that of (Bohm, et al, 1986) work [283].

**Table 2:** Reported *Nymphoides* species isolated flavonoids in different parts various extraction solvents.

<i>Nymphoides</i> species	Plant part	Extraction solvent	Isolated flavonoids	Quantity of each flavonoid	Ref.
<i>Nymphoides indica</i> (L.) Kuntze	Leaves	Crud extract fractionation solvents (methanol, ethyl acetate and <i>n</i> -butanol)	3,7-Di-O-methylquercetin-4'-O- $\beta$ -glucoside. 3-O-Methylquercetin-7-O- $\beta$ -glucoside 3,7-di-O-methylquercetin	-----	[106, 263, 266]
<i>Nymphoides indica</i>	Rhizomes	Hydroalcoholic extract	3,7-di-O-methylquercetin-4'-O- $\beta$ -glucoside. 3,7-Di-O-methylquercetin	-----	[281]
<i>Nymphoides Indica</i> Kuntze	Whole plant	95% methanolic extract: flavonoid fraction	- Quercetin 3,7-dimethyl ether 4'-glucoside	-----	[282]
<i>Nymphoides hydrophylla</i>	Leaves, seeds and whole plant part	-----	Kaempferol. Allantoin.	-----	[280]
<i>Nymphoides cristata</i>	Leaves	Methanolic hydrolysates	Myricetin (major flavonoid)	1099.85 $\pm$ 37.03 $\mu$ g/g DW	[271]
			Quercetin	116.53 $\pm$ 26.66 $\mu$ g/g DW	
			Kaempferol	107.41 $\pm$ 5.35 $\mu$ g/g DW	
<i>Nymphoides indica</i> (L.) Kuntze	Leaves	90% methanolic extract	3,7-dimethoxy Taxifolin. 3,7-dimethoxy Taxifolin-4'-O glycoside. 3-methoxy Taxifolin-7-O-glycoside. 6-methoxy-Taxifolin-3-O-glycoside.	-----	[269]
<i>Nymphoides hydrophylla</i>	Whole plant	Aqueous and ethanolic extracts	Quercetin and kaempferol and their glycosides	-----	[282]

**Table 3:** The flavonoids aglycones and glycosides derivatives of *Nymphoides* species modified from that of (Bohm, et al, 1986) work <sup>[283]</sup>.

Type of flavonoid	<i>N. cordata</i>	<i>N. crenata</i>	<i>N. cristata</i>	<i>N. exigua</i>	<i>N. fallax</i>	<i>N. geminata</i>	<i>N. grayana</i>	<i>N. indica</i>	<i>N. peltata</i>
<b>Aglycone</b>	Quercetin Kaempferol	Quercetin kaempferol	Quercetin kaempferol	kaempferol	Quercetin Kaempferol 7-O-methylquercetin 3,7-O-methylquercetin	Quercetin Kaempferol Isorhamnetin 7-O-methylquercetin 3,7-O-methylquercetin 3',7-O-methylquercetin	Quercetin	Quercetin Kaempferol Isorhamnetin 7-O-methylquercetin 3,7-O-methylquercetin	quercetin
<b>Mono-glycoside</b>	Kaempferol-3-O-glucoside Kaempferol-3-O-galactoside Kaempferol-3-O-rhamnoside Quercetin-3-O-glucoside Quercetin-3-O-galactoside Quercetin-3-O-rhamnoside	Kaempferol-3-O-glucoside Kaempferol-3-O-galactoside Kaempferol-3-O-arabinoside Quercetin-3-O-glucoside Quercetin-3-O-galactoside Quercetin-3-O-arabinoside	Kaempferol-3-O-glucoside Quercetin-3-O-glucoside Quercetin-3-O-arabinoside	Quercetin-3-O-glucoside	Kaempferol-3-O-glucoside Quercetin-3-O-glucoside Quercetin-4'-O-glucoside Quercetin-3-O-arabinoside Quercetin-3-O-rhamnoside 7-O-methyl-Quercetin-3-O-glucoside 7-O-methyl-Quercetin-3-O-rhamnoside 7,3'-O-dimethyl-Quercetin-3-O-glucoside Acyl Quercetin-3-O-glucoside deivative	Quercetin-3-O-glucoside Quercetin-4'-O-glucoside Quercetin-3-O-galactoside Quercetin-3-O-arabinoside Quercetin-3-O-rhamnoside 7-O-methyl-Quercetin-3-O-glucoside 3,7-O-dimethyl-Quercetin-4'-O-glucoside Acyl Quercetin-3-O-glucoside deivative	Kaempferol-3-O-glucoside Quercetin-3-O-glucoside Quercetin-3-O-arabinoside 7-O-methyl-Quercetin-3-O-glucoside 3,7-O-dimethyl-Quercetin-4'-O-glucoside	Kaempferol-3-O-glucoside Kaempferol-3-O-arabinoside Quercetin-3-O-glucoside Quercetin-3-O-arabinoside 7-O-methyl-Quercetin-3-O-glucoside 3,7-O-dimethyl-Quercetin-4'-O-glucoside	Quercetin-3-O-glucoside Quercetin-3-O-arabinoside
<b>di-glycoside</b>	Kaempferol-3-O-diglycoside Kaempferol-3-O-gluco-rhamnoside Quercetin-3-O-diglycoside	Quercetin-3-O-gluco-arabinoside	Kaempferol-3-O-gluco-arabinoside Quercetin-3-O-gluco-arabinoside	Quercetin-3-O-gluco-arabinoside Quercetin-3-O-gluco-rhamnoside	Quercetin-3-O-gluco-arabinoside 7-O-methyl-Quercetin-3-O-gluco-galactoside	Kaempferol-3-O-diglycoside Kaempferol-3-O-gluco-rhamnoside Quercetin-3-O-diglycoside Quercetin-3-O-gluco-rhamnoside Isorhamnetin-3-O-glucoside	Kaempferol-3-O-gluco-galactoside Quercetin-3-O-gluco-arabinoside 7-O-methyl-Quercetin-3-O-diglycoside	Kaempferol-3-O-gluco-arabinoside Quercetin-3-O-gluco-arabinoside Isorhamnetin-3-O-glucoside	Quercetin-3-O-gluco-arabinoside Quercetin-3-O-gluco-rhamnoside Quercetin-3-O-galacto-rhamnoside Quercetin-3-O-gluco-galactoside acyl derivative

## CONCLUSIONS:

Aquatic plants are versatile source of phytochemicals that are of significant biological influences particularly, the flavonoids and their glycosidic derivatives distributed in different plant parts including fruits, seeds, leaves, flowers, stem, roots and rhizomes. These phytochemicals have been thoroughly reported to exploit a broad spectrum of biological influences including, antioxidant, antihyperlipidemic, antiemetic, antitumor, anti-inflammatory, immune-modulatory, antimicrobial, antidiabetic, antiallergic, hepatoprotective, other organs-protective, antiaging as well as enzymes inhibitory influences that contribute to these plants reported biological effects as well as folkloric uses, besides counteracting snakes bit toxicities. Flavonoids are reported to inhibit wide

range of various enzymes including xanthine oxidase, protein kinase C, phosphodiesterase, 5 $\alpha$ -reductase, topoisomerase II and protein tyrosine phosphatase 1B (PTP1B) enzymes. Most of the reported biological influences are reported to be expressed by quercetin, kaempferol, isorhamnetin, and their glycosidic derivatives, particularly, rutin that exhibit antibacterial, antifungal, antiparasitic as well as antiviral effect against broad spectrum of microbes in addition to their strains. The various quercetin glycosides are also reported to exploit such formerly mentioned activities, hence, could be considered as essential contributors to these biological influences especially antineoplastic influences of wide range of tumors such as colon, lung, metastatic, colorectal-lung, ovarian, melanocytic tumors...etc via modulation /interference with

various molecular mechanisms. In this review, we summarized the reported flavonoids types, content and factors affecting their extracts contents of three aquatic plants Nuphar, Najas and Nymphoides detected in the Iraqi central marshlands, in provenance of Thi-Qar. Surveying the phytochemical investigations regarding Nuphar species of reported abundance of polyphenolic compounds content including phenolic acids, flavonoids like flavonols and flavonones, particularly, in their leaves. However, hydrolysable tannins and phenolic acids are identified and quantified in seedling plant and roots however, flavonoids/their derivatives types and quantities in various parts extracts are not reported to the extent of our knowledge although they are presumed to contribute to the reported biological influence of the plant on one hand. On the other hands, reports regarding *Najas* species, few reports have identified the existence of flavonoids as well as other phenolic compounds, although, total quantification to the phenolic compounds, flavonoids and tannins are reported rather than identifying the individual flavonoid in the plant extracts. Only single report demonstrates the total total phenolic, flavonoids and tannin contents of ethyl acetate extract of *Najas minor* according to our survey. Regarding *Nymphoides* species, numerous reports have demonstrated the abundant existence of phenolic phytochemicals including phenolic acids, flavonoids, coumerins and tannins besides the existence of other classes of secondary plant metabolites. Nevertheless, the extraction level flavonoids as lipophilic compounds as well as their much polar glycosidic derivatives is depending on the solvent polarities, where, the greatest levels of polyphenolic compound mostly in the polar (like methanol) to intermediate polarity organic solvents (like ethylacetate) which are major contributors besides other plant secondary metabolites to these extract's antioxidant, antidiabetic, antiglycation, antibacterial and  $\alpha$ -glucosidase inhibitory effects. The greatest total phenolic and total flavonoids compounds are reported in ethyl acetate extract of the leaves of *Nymphoides indica* with concentrations of 43.1 mg GAE/g and 73.44 mg RUE/g, while, in the ethanolic extract of the *Nymphoides hydrophylla* whole plant at concentrations of 79.43 mg GAE/g and 197.21 mg QE/g respectively. In general in most of *Nymphoides* species the ethanolic extract quercetin, methylquercetin and kaempferol flavonoids/their derivatives are identified individual flavonoids/quantified to be more than one fold of that in the aqueous extracts explaining the enhanced magnitudes of antioxidant, antiaging, anti-proliferative, antiglycation, anti-inflammatory, anti-HIV antiviral, antimicrobial, and,  $\alpha$ -glucosidase inhibitory influences. Remarkably, Quercetin/methyl quercetin 4'-O- and 7-O-glycosides are the majorly dominant/quantity abundant flavonoids in the *Nymphoides* species extracts followed by kaempferol/its glycosides. In addition, in other than *Nymphoides indica*, elevated degrees of methylation is noticed at C3, C7 and C3' hydroxyl groups. Furthermore, isorhamnetin, 7-O-methylquercetin, 7-O-methylkaempferol, 3,7-di-O-methylquercetin, and 7,3'-di-O-methylquercetin are detected in nine *Nymphoides* species including *N. indica*. Unfortunately, to our survey with the exception of *Nymphoides cristata* leaves methanolic hydrolysate, the identified flavonoids in various plant parts extracts are not quantified. Finally, the manner/position of glycosylation as

well as glycosides sugar residues acylation vary among the *Nymphoides* species. In general, single 3-O- or di 3,4'-O-glycosylation pattern is noticed in kaempferol, quercetin and isorhamnetin which are identified at two *Nymphoides* species including *N. geminate* and *N. indica*, while, 4'-O-glucosides is identified in *N. indica*, *N. fallax*, *N. grayana*, and *N. geminate*, although, 3-O-glycosylation is identified in other species. Nevertheless, glucoses and galactose are mostly the first sugar moiety glycoside in monoglycosylated flavonoids, while, the inner sugar moiety linked to mostly to rhamnose as an outer sugar moiety in diglycoside derivatives. The multiply diverse glycosylation, methylation as well as acylation pattern of *Nymphoides* species flavonoids may explains their identification in various plant part/extracts besides the variation in their biological activities potentials.

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