Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 33, issue 3, 2023, pp. 109 - 115

GEMMOTHERAPY EXTRACTS WITH QUERCETIN AND ITS DERIVATIVES

Elisabeta CHIŞE[1], Neli-Kinga OLAH[1,2], Ramona Flavia BURTESCU[2], Daniela HANGANU[3*], Simona MIREL[3], Adriana DĂRĂBAN[1], Ioana HEPCAL CUC[1], Maria JOLJI[6], Melinda HÉJJA[6], Viviane B. BOTA[4,5], Endre MÁTHÉ[4,6], Violeta TURCUŞ[4,5*]

[1]Faculty of Pharmacy, "Vasile Goldiș" Western University of Arad, 310048, Romania
[2]SC PlantExtrakt SRL, Rădaia, Cluj, 407059, Romania
[3]Department of Pharmacognosy, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca 400010, Romania
[4]Department of Biology, "Vasile Goldiș" Western University of Arad, 310048, Romania
[5]National Institute for Economic Research "Costin C. Kiritescu" of the Romanian Academy/ Centre for Mountain Economy (CE-MONT), Vatra Dornei, Romania
[6]Institute of Nutrition, University of Debrecen, H-4032, Hungary

Abstract: Quercetin is one of the most common polyphenol worldwide, named after the oak forest – *quercetum*. It is considered one of the most powerful antioxidants due to its five phenolic groups, respectively, the ɣ-pyrone cycle. This flavonoid and its glycosylated derivatives, such as rutoside, hyperoside, quercitrin, and iso-quercitrin, are also present in the extracts obtained from the buds and young shoots of different species, extracts that are therapeutic tools for the new branch of phytotherapy named gemmotherapy or meristem-therapy. In the pandemic context the quercetin and its derivatives were successfully used to improve the side/late effects of SARS-CoV-2 infection. Our study involved the extracts from buds of hazel (*Corylus avellana)*, sweet chestnut (*Castanea sativa*), and the young shoots from honeysuckle (*Lonicera nigra*), dog-rose (*Rosa canina*), lingonberry (*Vaccinium vitis-idaea*), and European blackberry (*Rubus fruticosus*). Quercetin and its derivatives were identified and quantified by the HPLC method. The total flavonoids were determined by the spectral method. The highest quercetin-containing gemmotherapy extracts were obtained from the sweet chestnut and hazel buds, respectively, from Honeysuckle and Lingonberry young shoots. Due to their rich quercetin content, these extracts were proposed for the complementary treatment of SARS-CoV-2 infections and post-COVID symptoms.

Keywords: quercetin; gemmotherapy extracts; Hazel buds; Sweet chestnut buds; Honeysuckle young shoots; Lingonberry young shoots; SarsCov-2 infection.

INTRODUCTION

Quercetin is an important flavonol, from the flavonoid class, being a polyphenol known since 1857, when its name was given after the Latin term for oak forest, *quercetum*. Since then, it is one of the most studied flavonoids, being widespread in all vegetal kingdom, from leaves to fruits, seeds, etc. (Kim *et al.*, 2018; D'Andrea, 2015).

In time, the studies proved this flavonoid has important therapeutic value, as polyphenols possess high antioxidant potential, which is achieved by different mechanisms of action. Quercetin can be oxidised by free radicals, stabilising the ROS and RNS, resulting in reduced radical reactivity. The same flavonoid aglycone, quercetin, inhibits the activity of xanthine oxidase, a major source of active free oxygen radicals in ischemic conditions. The free oxygen radicals released by leucocyte immobilisation by adhering to the endothelial wall can be scavenged by quercetin and thus reduce the tissue damage, but also the inflammation and mast cell degranulation. The antioxidant effect of quercetin is also determined by its iron-chelating and iron-stabilising properties (Kim *et al.*, 2018; Nijveldt *et al.,* 2001). Quercetin prevents lipid peroxidation, at the same time enhancing the expression and the level of endogenous antioxidant enzymes, like glutathione transferase, aldo-keto reductase, and superoxide dismutase (D'Andrea, 2015; Batiha *et al.,* 2020; Dengyu *et al.,* 2020).

Due to its antioxidant potential, quercetin has beneficial effects on different systems and organ systems of the body. It reduces the oxidative stress induced in diabetes mellitus, in cancer, at the endothelium level, and has antiaging and hepatoprotective effects (Kim *et al.,* 2018; D'Andrea, 2015; Nijveldt *et al.,* 2001; Batiha *et al.,* 2020; Dengyu *et al.,* 2020).

Quercetin, with its high antioxidant potential, also presents anti-inflammatory, cardioprotective, and neuroprotective effects (David *et al.,* 2016). *In vitro* studies on human hepatocyte-derived cell line demonstrated that this flavonoid significantly reduces the NO synthase, COX-2, and C-reactive protein levels, showing an anti-inflammatory effect. It inhibits platelet aggregation and, through its antioxidant and NO-reducing action, it also exhibits vasorelaxant properties. At a nervous system level, it protects the neurons against the neurotoxins' negative effects and limits neurodegeneration (David *et al.,* 2016).

The same quercetin was also claimed to be responsible for antiviral and antimicrobial effects. Formulation with quercetin has been demonstrated to be

***Correspondence**: Violeta Turcuș, Department of Biology, "Vasile Goldiș" Western University of Arad, 310048, Romania, email: violeta_buruiana@yahoo.com; Daniela Hanganu, Department of Pharmacognosy, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca 400010, Romania, email: dhanganu@umfcluj.ro*

potent against hepatitis C, influenza-A, and other specific viruses that attack the respiratory system (Weinjiao *et al.,* 2016; Qiu *et al.,* 2016). Quercetin fights against infections with *E. coli*, *Salmonella enterica*, and *Listeria monocytogenes,* exhibiting bacteriostatic effect (Maalik *et al.,* 2014), and promotes immunity by direct regulation of basic functional properties of immune cells (Li *et al.,* 2016).

Quercetin has low bioavailability because of low absorption, rapid metabolism and elimination, but its glycosides are better absorbed due to the sugar moieties. These glycosides are hydrolysed by the intestinal bacteria to quercetin, which is absorbed at this level or is transformed into different phenolic compounds with different biological activities (Li *et al.,* 2016). The studies have demonstrated that rutoside, iso-quercetin, and quercitrin have better absorption and bioavailability than the quercetin aglycone, exhibiting in the body the biological effects of the aglycone (Li *et al.,* 2016; Kasikci *et al.,* 2016; Almeida *et al.,* 2018; Li *et al*., 2021).

Quercetin was recently involved as a potential therapeutic tool in the prevention and improvement of different symptoms occurring during and after SARS-CoV-2 infections. A clinical trial performed in Italy shows that the patients treated with a quercetin preparation pass easier and more rapid through the infection, shortening the time of conversion of tests from positive to negative and, at the same time, reducing the severity of symptoms (Di Pierro *et al.,* 2021; Aucoin *et al*., 2020). These positive results can be due to the quercetin anti-inflammatory effect by inhibition of NLRP3 inflammasome regulators: TXNIP, SIRT1, and NRF2 (Saeedi-Boroujeni *et al*., 2021). But also, other mechanisms of action are involved in the success of quercetin in the fight against the COVID-19 pandemic. Quercetin was demonstrated to be a potent NRF2 agonist that reduce or inhibit the replication of coronavirus into the lung cells, inhibits the entry of virion into the host cell, has antiaggregant effect by inhibiting the plasma protein disulfide isomerase and, last but not least, inhibits the pro-inflammatory signals of pathways activated by nuclear factor kappa B (NF-kB) and interleukin-6 (IL-6) (Manjunath *et al.,* 2021). Other studies reveal that quercetin blocks like a key the ACE2 receptors involved in the virus entrance mechanism into the host cells (Jain et al., 2020). A more potent antiviral effect seems to be associated the quercetin when it is administered with vitamin C (Colunga Biancatelli *et al.,* 2020).

All these results regarding quercetin and its derivatives indicate the high value of their natural sources. This was the aim for which we have screened several special extracts from trees and shrubs' buds, and young shoots to evaluate from the point of view of the content in quercetin and its derivatives.

Gemmotherapy is the name of a new branch of phytotherapy that uses just those parts of plants that contain mainly undifferentiated, meristematic tissues, with a higher therapeutic potential due to the different phytochemical profile in comparison with adult parts of plants used by classical phytotherapy. The extracts used in gemmotherapy are obtained from fresh buds and young shoots, harvested at a very well-defined time of their development for an optimal biological effect that is at a deep, molecular level, but is also mild and natural. These young parts of plants are rich in primary metabolites, but also in secondary ones and mainly in polyphenols (Pitera *et al*., 2018; Ledoux *et al.,* 2014; Tetau, 1998).

The goal of this study was to demonstrate that gemmotherapy extracts used to improve the symptoms of different respiratory system diseases contain quercetin and quercetin derivatives, which can be valuable in the convalescence or prevention of complications in SARS-CoV-2 infections.

MATERIALS AND METHODS

Vegetal material and the preparation of gemmotherapy extracts taken into study

In this study, we used extracts prepared by PlantExtrakt Ltd., Rădaia, Cluj, Romania (www.plantextrakt.ro; contact@plantextrakt.ro). We used the extracts from hazel and sweet chestnut buds, respectively, from honeysuckle, dog rose, lingonberry, and blackberry young shoots. Except for the sweet chestnut, all other vegetal materials were harvested from the wild flora of the mountains near Cluj, Romania, from February to June 2020. The sweet chestnut buds were collected from a culture situated in a protected area in Cluj County in April 2020. From all vegetal materials, samples were taken for identification, performed at the PlantExtrakt company quality control laboratory. For each species, voucher specimens were retained in the company's herbarium.

The extracts were prepared according to the French and European Pharmacopoeias in a mixture of 96 % vol. ethanol and 100 % glycerol (1:1) (French Pharmacopoeia, 11th ed., 2020; European Pharmacopoeia, 10th ed., 2021). The vegetal raw material was processed in a fresh state, after being cut, mixed with the solvent using a ratio of 1:20, plant material – solvent. The extraction was performed by cold maceration, by mixing periodically the mixture of plant material with the solvent. After 20 days, the liquid was decantated, and the plant material was pressed at a maximum of 400 atm. The extraction liquids were mixed, and these final solutions represent the gemmotherapy extracts.

The solvents used for extraction are of pharmaceutical grade, purchased from SC Coman Prod SRL, Ilfov, Romania, and Spiga Nord, Italy. The collection of the plant materials was made according to the Good Agricultural Practices for Collection, taking into consideration the preservation of biodiversity and Eco certification Ro-008.

Determination of total flavonoids by UV-Vis spectrophotometry

The determination of total flavonoids was performed according to Romanian Pharmacopoeia, 10th ed., 1993. The determinations were performed on a Cintra 101 spectrophotometer (GBC, Australia). To 1 ml aliquots of each extract were added 3 ml of 2.5 % aluminium chloride solution and 5 ml 10 % sodium acetate solution. The mixtures were diluted to 25 ml with methanol. The

Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 33, issue 3, 2023, pp. 109 - 115

blank solutions were prepared identically using 8 ml of water in place of the aluminium chloride and sodium acetate solutions. In the same manner were prepared also the standard solutions containing 2-25 µg/ml quercetin. These solutions were used to build the calibration curve that has a correlation factor of 0.9997 and a limit of quantification of 1.47 µg/ml. All determinations were performed in triplicate, and Excel software from Microsoft Office was used for data statistics. All reagents were of analytical grade, purchased from Merck, Germany. The standard quercetin was obtained from Phytolab, Germany.

Determination of quercetin and its derivatives by HPLC

The determination of individual flavonoids was performed by liquid chromatography using a Shimadzu Nexera-I HPLC apparatus. The separation was carried out on a Luna C18, silicagel-C18 150 x 4.6 mm x 3 µm column using gradient elution with a mixture of 0.1 % formic acid solution with pH corrected to 2.5 and methanol. The composition of the mobile phase varies from 5 % methanol to 25 % in the first 3 minutes, then to 37 % until the minute 9, to 54 % until the 18th minute, and to 95 % until the 26th minute. The composition of the mobile phase was maintained for 4 minutes and then reached 5 % methanol until the end of analysis (minute 35th). The separation was performed using a flow rate of 0.5 ml/minute. From each extract, diluted 1 to 10 with methanol, 10 µl was injected. For detection, a DAD spectrophotometer was employed that recorded all data in the range of 190-660 nm. The chromatogram for flavonoids identification and quantification was recorded at 360 nm. As standards were used quercetin, hyperoside, rutoside, and quercitrin. The calibration curves data for all these flavonoids are presented in Table 1. All determinations were performed in triplicate, and data were analysed using Excel software from the Microsoft Office package (Criste *et al.,* 2020). All solvents were of HPLC grade, purchased from Merck, Germany, and the standards from Phytolab, Germany.

Table 1.

Data of calibration curves

Standard	Concentration range, ug/ml	Calibration curve equation	Correlation factor R^2	Detection limit, ug/ml	Quantification limit, ug/ml
Quercetin	90-650	A = 35376*c-95138	0.9995	10.8	16.1
Quercitrin	40-330	A = 30871*c-229685	0.9948	22.3	37.2
Hyperoside	60-510	A = 35253*c-185515	09979	10.5	21.0
Rutoside	60-510	A = 34187*c+67369	0.9985	2	7.9

RESULTS AND DISCUSSIONS

The chromatograms of the extracts recorded at 360 nm are presented in Figures 1 and 2. It can be observed that the presence of quercetin in all extracts is accompanied by different derivatives of it. The rutoside could be identified in all extracts except the honeysuckle young shoots extract. This extract contains quercitrin. The hyperosid was present in hazel buds and lingonberry young shoots extracts. The identification was based on the comparison of retention times and UV-Vis spectra shape and maximum absorbances between standards and the compounds separated from the extracts.

Generally, the content of quercetin derivatives in the studied extracts is higher than in quercetin. The quantification data are presented in Table 2.

Table 2.

Quantification results

Extract from	Quercetin, ug/ml	Rutoside, ug/ml	Hyperoside, ug/ml	Quercitrin, ug/ml	Total flavonoids expressed in quercetin, mg/ml
Hazel buds	31.83 ±0.015	10.15 ±0.005	121.30 ±0.084	-	0.44±0.032
Sweet chestnut buds	54.24 ±0.027	62.85 ±0.047	-	-	0.33±0.028
Honeysuckle young shoots	34.15 ±0.010	-	-	223.65 ±0.067	0.34±0.015
Dog rose young shoots	30.11 ±0.019	83.94 ±0.075	-	-	0.81±0.081
Lingonberry young shoots	48.52 ±0.008	3.22±0.002	183.90 ±0.099		0.68±0.051
Blackberry young shoots	30.67 ±0.012	< 7.90	-	-	0.20±0.017

Note: Values represent the mean ± standard deviations of three independent measurements.

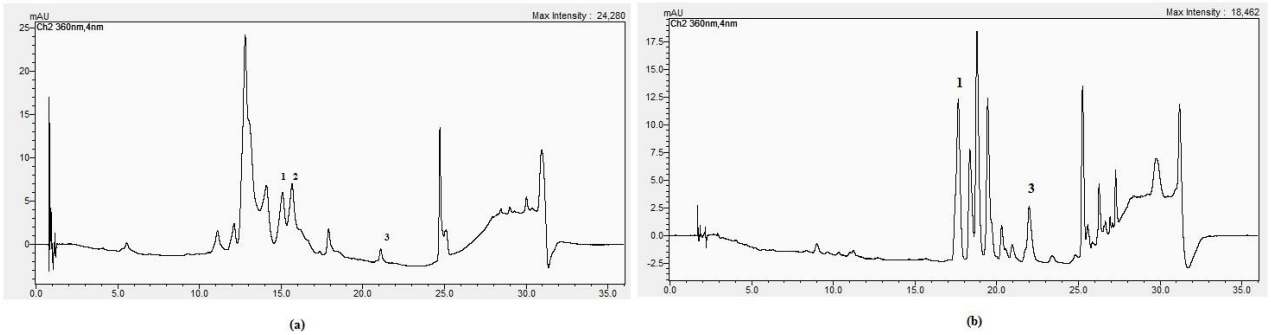

Fig. 1. The HPLC chromatograms of the buds' extracts obtained from (**a**) hazel; (**b**) sweet chestnut. 1 = rutoside (17.4 min; 257 and 356 nm); 2 = hyperoside (17.7 min; 256 and 356 nm); 3 = quercetin (22 min; 255 and 371 nm).

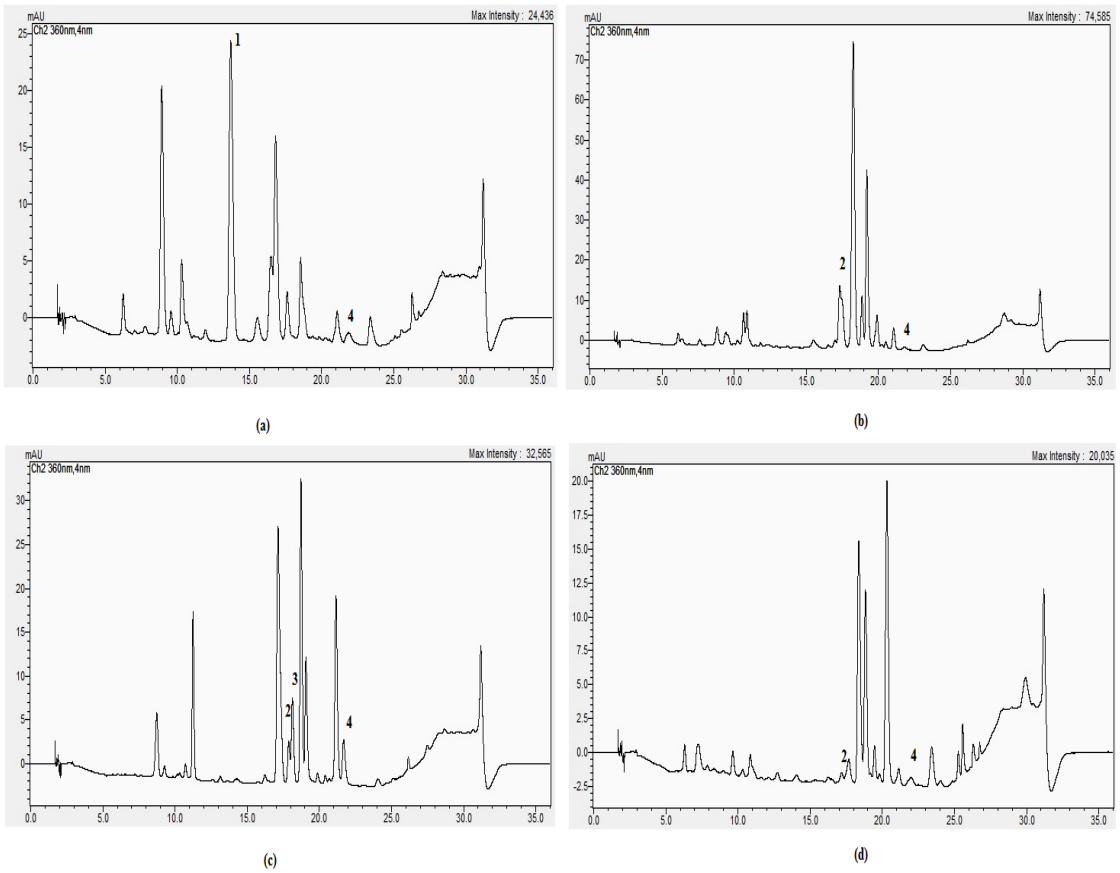

Fig. 2. The HPLC chromatograms of the young shoots' extracts obtained from (**a**) honeysuckle; (**b**) dog-rose; (**c**) lingonberry; (**d**) blackberry. 1 = quercitrin (14.2 min; 257 and 350 nm); 2 = rutoside (17.4 min; 257 and 356 nm); 3 = hyperoside (17.7 min; 256 and 356 nm); 4 = quercetin (22 min; 255 and 371 nm)

The results show that the highest content of quercetin is in the sweet chestnut buds' extract, even if this extract has a relatively low total flavonoid content. This gemmotherapic extract also contains rutoside in a slightly higher amount. The dog rose young shoots extract has the highest content in total flavonoids, but from these, the quercetin and rutoside represent only 15 %. A relatively high amount of flavonoids and quercetin is found in the lingonberry young shoots gemmotherapic extract. If we calculate the percentage of quercetin from the total flavonoids amount, we can see that the richest extracts in these compounds are the sweet chestnut (16.20 %) and blackberry young shoots extracts (15.66 %). Medium-rich in quercetin are the honeysuckle young shoots (9.95 %) and hazel buds (7.20 %) gemmotherapic extracts.

The scientific literature is very poor in regards to the phytochemical composition of gemmotherapic extracts that have been used more frequently in the last 40 years. For this reason, it is very difficult to compare our results with those of other studies. The results obtained from the analysis of these specific extracts are reported here for the first time, according to a comprehensive review of relevant scientific databases. Notwithstanding this fact, an effort is made to compare these results with those obtained for leaves or other plant materials from the studied species.

The hazel buds are rich in quercetin-derived flavonoids; from the total flavonoid content, 37.1 % is represented by quercetin, rutoside and hyperoside. A study on the valorisation of *Corylus avellana* husks, a waste from the food industry, underlined that this waste is rich in polyphenols, with identified flavonoids including derivatives of quercetin, kaempferol, and luteolin (Cabo *et al*., 2021). Amaral *et al*. (2005) have found in the leaves of different *Corylus avellana* cultivars from Portugal quercetin, myricetin, and kaempferol derivatives.

From all studied gemmotherapy extracts, those obtained from sweet chestnut buds proved to have the highest quercetin level, 35,5 % of total flavonoids are represented by quercetin and its derivative, rutoside. The sweet chestnuts have edible seeds processed in the food industry, resulting in a lot of waste that has been shown to be rich in polyphenols, mainly in quercetin and myricetin-glycosides from the flavonoid class. These polyphenols exhibit good antioxidant and antimicrobial activities (Silva *et al*., 2020).

The *Lonicera* species were intensively studied from the beginning of the COVID-19 pandemic, given their potential antiviral effect. The *Lonicera nigra* buds' extract is rich in quercitrin and contains a significant quantity of free quercetin, with 75.8 % of the total flavonoid content of this extract represented by quercetin and quercitrin. Unfortunately, the studies on *Lonicera nigra*, and especially on its young shoots, are scarce. A group of researchers from the Czech Republic has studied the *Lonicera edulis* edible fruits and identified quercetin and quercitrin along with rutoside and other polyphenols (Sochor *et al*., 2014).

The dog rose is a well-known medicinal species, a rich source of vitamin C, but its young shoots are understudied. The hips of *Rosa canina* are rich in rutoside and hyperoside; meanwhile, the leaves are not as rich in flavonoids as other Rosa species studied by D'Angiolillo *et al*. (2018), respectively by Kerasioti *et al.* (2019). A study aimed to explore the *Rosa canina* young shoots extract antimicrobial activity presents that this extract is rich in polyphenols, mainly in flavonoids, presenting quercetin and its derivatives: hyperoside, isoquercetin, rutoside, and quercitrin (Orodan *et al.,* 2016). Our study revealed the presence in the dog rose gemmotherapic extract of quercetin and rutoside, accounting for 14 % of the total flavonoid content.

The lingonberry young shoots extract is rich in hyperoside, 34.7 % of the total flavonoids being represented by quercetin, hyperoside, and rutoside. A study that evaluates the geographical effect on phenolics content in *Vaccinium vitis-idaea* leaves identified quercetin and kaempferol derivatives in its composition (Vilkickyte *et al.,* 2021).

From all studied samples, the blackberry young shoots extract presented the lowest concentration of flavonoids and quercetin. Studies revealed that the blackberry fruits contain quercetin and rutoside, which contribute to the fruits' anti-diabetic, anti-inflammatory, and antimicrobial effects (Zia-Ul-Haq *et al.,* 2014; Bhuyan *et al.,* 2021).

Despite being few in numbers, the found references are in accordance with our results, sustaining the use of buds and young shoots of the species taken into study as valuable sources of quercetin and its derivatives.

According to the physicians' observations, the main gemmotherapic extracts with special biological effects on the respiratory system include the type of extracts taken in our study. The hazel (*Corylus avellana* L.) buds extract increases the elasticity of lung tissues, decreasing the tendency to sclerosis, and is recommended to increase the lungs' resistance in pneumonia. The sweet chestnut (*Castanea sativa* Mill.) buds extract stimulates the lymphatic circulation, and at the lung level, helps to expectorate the excessive mucus from the bronchus. The honeysuckle (*Lonicera nigra* L.) gemmotherapy extract exerts an anti-inflammatory effect in the case of respiratory tract infections. The dog rose (*Rosa canina* L.) young shoots extract is a rich source of vitamin C, together with the polyphenols, being useful in the prevention of flu, stimulating the immune system, and reducing inflammation. It is often recommended for children to prevent flu relapses. The lingonberry (*Vaccinium vitis-idaea* L.) young shoots extract is one of the most powerful antibacterial gemmotherapic extracts, being efficient in the treatment of *E. coli* infections, and given its antioxidant activity, it protects the lungs and circulatory system, preventing the atherosclerotic damage of the endothelium. The European blackberry (*Rubus fruticosus* L.) young shoots extract exerts an anti-sclerotic effect, increasing the lungs' resistance in case of chronic obstructive broncho-pneumonia, and protecting the bronchus (Pitera *et al.,* 2018; Ledoux *et al.,* 2014; Tetau, 1998).

The above-mentioned clinical observations could be related to flavonoids, as the presence of quercetin in all these gemmotherapy extracts could be, among others, a valuable adjuvant in reducing the risk of infection, and the complications in case of infections or in the improvement of pathologies after the infection with the SARS-CoV-2 virus. Moreover, it remains a major challenge to elucidate the molecular mechanisms underlying the putative protective functions of quercetin-containing gemmotherapy extracts.

CONCLUSIONS

The present study demonstrated that the gemmotherapy extracts examined contain valuable therapeutic flavonoids. Based on their quercetin and derivative content, these extracts could be recommended for preventing complications from viral infections and for convalescence after SARS-CoV-2 infection, in light of existing clinical observations.

AUTHORS CONTRIBUTIONS

Conceptualization, E.C., N.K.O., E.M., D.H. and E.M. methodology, R.F.B., I.H.C. and V.B.B.; data collection A.D., M.J. and M.H..; data validation, E.C., D.H., S.M., E.M. and V.T..; data processing E.C., N.K.O., D.H. and A.D.; writing—original draft preparation, E.C., N.K.O., D.H. and E.M.; writing—review and editing, V.B.B. and V.T.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Almeida, A.F.; Borge, G.I.A.; Piskula, M.; Tudose, A.; Tudoreanu, L.; Valentova, K.; Williamson, G.; Santos, C.N. Bioavailability of quercetin in humans with a focus on individual variation. Comprehensive Rev. Food Sci. Food Safety 17, 714-731, 2018. http://dx.doi.org/10.1111/1541-4337.12342

Amaral, J.S.; Ferreres, F.; Andrade, P.B.; Valentao, P.; Pinheiro, C.; Santos, A.; Seabra, R. Phenolic profile of hazelnut (*Corylus avellana* L.) leaves cultivars grown in Portugal. Nat. Prod. Res. 19 (2), 157-163, 2005. http://dx.doi.org/10.1080/14786410400017047 78

Aucoin, M.; Cooley, K.; Saunders, P.R.; Cardozo, V.; Remy, D.; Cramer, H.; Abad, C.N.; Hannan, N. The effect of quercetin on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: a rapid review. Adv. Integr. Med. 7 (4), 247-251, 2020. http://dx.doi.org/10.1016/j.aimed.2020.07.007

Batiha, G.E-S.; Beshbishy, A.M.; Ikram, M.; Mulla, Z.S.; Abd El-Hack, M.E.; Taha, A.E.; Algammal, A.M.; Elewa, Y.H.A. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: quercetin. Foods 9, 374, 2020. http://dx.doi.org/10.3390/foods9030374

Bhuyan, B.; Dutta, A. A review on the phytochemical, pharmacological, and traditional profile on the *Rubus* genus in the north-eastern and western parts of India. Curr. Trends Pharm. Res. 8 (1), 73-87, 2021.

Cabo, S.; Aires, A.; Carvalho, R.; Pascual-Seva, N.; Silva, A.P.; Goncalves, B. Corylus avellana L. husks an underutilized waste but valuable source of polyphenols. Waste Biomass Valor. 12, 3629-3644, 2021. http://dx.doi.org/10.1007/s12649-020-01246-4

Colunga Biancatelli, R.M.L.; Berrill, M.; Catravas, J.D.; Marik, P.E. Quercetin and vitamin C: an experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). Front. Immunol. 11, 1451, 2020. http://dx.doi.org/10.3389/fimmu.2020.01451

Criste, A.; Urcan, A.C.; Bunea, A.; Pripon Furtuna, F.R.; Olah, N.K.; Madden, R.H.; Corcionivoschi, N. Phytochemical composition and biological activity of berries and leaves from four Romanian sea buckthorn (*Hippophae rhamnoides* L.) varieties. Molecules 25, 1170, 2020. http://dx.doi.org/10.3390/molecules25051170

D'Angiolillo, F.; Mammano, M.M.; Fascella, G. Pigments, polyphenols and antioxidant activity of leaf extracts from four wild rose species grown in Sicily. Not. Bot. Horti. Agrobot. 46 (2), 402-409, 2018. http://dx.doi.org/10.15835/nbha46211061

D'Andrea, G. Quercetin: A flavonol with multifaceted therapeutic applications? Fitoterapia 106, 256-271, 2015. http://dx.doi.org/10.216/j.fitote.2015.09.018

David, A.V.A.; Arulmoli, R.; Parasuraman, S. Overviews of biological importance of quercetin: a bioactive flavonoid. Pharmacogn. Rev. 10(20), 84-89, 2016. http://dx.doi.org/10.4103/0973-7847.194044

Dengyu, Y.; Tiancheng, W.; Miao, L.; Peng, L. Quercetin: its main pharmacological activity and potential application in clinical medicine. Oxidative Med. Cel.Longevity, 1-13, 2020. http://dx.doi.org/10.1155/2020/8825387

Di Pierro, F.; Iqtadar, S.; Khan, A.; Mumtaz, S.U.; Chaudhry, M.M.; Bertuccioli, A.; Derosa, G.; Maffioli, P.; Togni, S.; Riva, A.; Allegrini, P.; Khan, S. potential clinical benefits of quercetin in the early stage of COVID-19: results of a second, pilot, randomized, controlled and open-label clinical trial. Int. J. Gen. Med. 14, 2807-2816, 2021. http://dx.doi.org/10.2147/IJGM.S318949

Jain, R.; Shukla, S.; Nema, N.; Panday, A.; Singh Gour, H. A systematic review: structural mechanism of SARS-CoV-2A and promising preventive cure by phytochemicals. J. Agr. Sci. Food Res. 11, 274, 2020. http://dx.doi.org/10.35248/2593-9173.20.11.274

Kasikci, M.B.; Bagdatlioglu, N. Bioavailability of quercetin. Curr. Res. Nutr. Food Sci. 4, 146-151, 2016. http://dx.doi.org/10.12944/CRNFSJ.4.Special-Issue-October.20

Kerasioti, E.; Apostolu, A.; Kafantaris, I.; Chronis, K.; Kokka, E.; Dimitriadou, C.; Tzanetou, E.N.; Priftis, A.; Koulocheri, S.D.; Haroutounian, S.A.; Kouretas, D.; Stagos, S. Polyphenolic composition of *Rosa canina*, *Rosa sempervirens* and *Pyrocantha coccinea* extracts and assessment of their antioxidant activity in human endothelial cells. Antioxidants 8, 92, 2019. http://dx.doi.org/10.3390/antiox8040092

Kim, J.K.; Park, S.U. Quercetin and its role in biological functions: an updated review. EXCLI J 17, 856-863, 2018. http://dx.doi.org/10.17179/excli2018-1538

Ledoux, F.; Gueniot, G. *La phytoembryotherapie, l'embryon de la gemmotherapie*; Editions Amyris SPRL, Bruxelles, Belgium, 2014.

Li, H.; Li, M.; Fu, J.; Ao, H.; Wang, W.; Wang, X. Enhancement of oral bioavailability of quercetin by metabolic inhibitory nanosuspensions compared to conventional nanosuspensions. Drug Delivery 28 (1), 1226-1236, 2021. http://dx.doi.org/10.1080/10717544.2021.1927244

Li, Y.; Yao, J.; Han, C.; Yang, X.; Tabassum Chaudhry, M.; Wang, S.; Liu, H.; Yin, Y. Quercetin, inflammation and immunity. Nutrients 8, 167, 2016. http://dx.doi.org/10.3390/nu8030167

Maalik, A.; Khan, F.A.; Mumtaz, A.; Mehmood, A.; Azhar, S.; Atif, M.; Karim, S.; Altaf, Y.; Tariq, I. Pharmacological applications of quercetin and its derivatives: a short review. Trop. J. Pharm. Res. 13 (9), 1561-1566, 2014. http://dx.doi.org/10.4314/tjpr.v13i9.26

Manjunath, S.H.; Thimmulappa, R.K. Antiviral, immunomodulatory and anticoagulant effects of quercetin and its derivatives: potential role in prevention and management of COVID-19. J. Pharm. Anal. 2021. http://dx.doi.org/10.1016/j.jpha.2021.09.009

Nijveldt, R.J.; van Nood, E.; van Hoorn, D.E.C.; Boelens, P.G.; van Norren, K.; van Leeuwen, P.A.M. Flavonoids: a review of probable mechanism of action and potential applications. Am. J. Clun. Nutr. 74, 418-425, 2001. http://dx.doi.org/10.1093/ajcn/74.4.418

Orodan, M.; Vodnar, D.C.; Toiu, A.M.; Pop, C.E.; Vlase, L.; Istudor, V.; Arsene, A.L. Phytochemical analysis, antimicrobial and antioxidant effect of some gemmotherapic remedies used in respiratory diseases. Farmacia 64 (2), 224-230, 2016.

Pitera di Clima, F.; Nicoletti, M. *Gemmoterapia. Fondamenti scientifici della moderna meristemoterapia.* 2nd ed.; Nuova Ipsa Editore srl, Palermo, Italy, 2018.

Qiu, X.; Kroeker, A.; He, S.; Kozak, R.; Audet, J.; Mbikay, M.; Chretien, M. Prophylactic efficacy of quercetin 3-b-O-D-glucoside against Ebola virus infection Antimicr. Ag. Chemother. 60 (9), 5182-5188, 2016. http://dx.doi.org/10.1128/AAC.00307-16

Saeedi-Boroujeni, A.; Mahmoudian-Sani, M.-R. Anti-inflammatory potential of quercetin in COVID-19 treatment. J. Inflam. 18, 3, 2021. http://dx.doi.org/10.1186/s12950-021-00268-6

Silva, V.; Falco, V.; Dias, M.I.; Barros, L.; Silva, A.; Capita, R.; Alonso-Calleja, C.; Amaral, J.S.; Igrejas, G.; Ferreira, I.C.F.R.; Poeta, P. Evaluation of the phenolic profile of *Castanea sativa* Mill. By-products and their antioxidant and antimicrobial activity against multiresistant bacteria. Antioxidants 9, 87, 2020. http://dx.doi.org/10.3390/antiox9010087

Sochor, J.; Jurikova, T.; Pohanka, M.; Skutkova, H.; Baron, M.; Tomaskova, L.; Balla, S.; Klejdus, B.; Pokluda, R.; Mlcek, J.; Trojakova, Z.; Saloun, J. Evaluation of antioxidant activity, polyphenolic compounds, amino acids, and mineral elements of representative genotypes of *Lonicera edulis*. Molecules 19, 6504-6523, 2014. http://dx.doi.org/10.3390/molecules19056504

Tetau, M. *Gemmotherapy, a clinical guide*. 2nd ed.; Editions du Detail Inc., Paris, France, 1998.

Vilkickyte, G.; Raudone, L. Phenological and geographical effects of phenolic and triterpenoid content in *Vaccinium vitis-idaea* L. leaves. Plants 10, 1986, 2021. http://dx.doi.org/10.3390/plants10101986

Weinjiao, W.; Richan, L.; Xianglian, L.; Jian, H.; Shibo, J.; Shuwen, L.; Jie, Y. Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry. Viruses, 8, 6, 2016. http://dx.doi.org/10.3390/v8010006

Zia-Ul-Haq, M.; Riaz, M.; de Feo, V.; Jaafar, H.Z.E.; Moga, M. *Rubus fruticosus* L.: constituents, biological activities and health related uses. Molecules 19, 10998-11029, 2014. http://dx.doi.org/10.3390/molecules190810998

European Pharmacopoeia ed. 10, EDQM, 2021.

Farmacopeea Romana, ed. 10, Editura Medicala, Bucharest, Romania, 1993.

Pharmacopee Francaise ed. 11, 2020, https://ansm.sante.fr/pharmacopee/preparations-homeopathiques-anglais