JURNAL FARMASI SAINS DAN KOMUNITAS
Journal of Pharmaceutical Sciences & Community

p-ISSN 1693-5683; e-ISSN 2527-7146

Vol. 21, No. 1, May 2024, pp. 44-50

Research Article

The Formulation of Effervescent Granules with *Oxalis dehradunensis* Raizada Ethanol Extract as an Antioxidant

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https://doi.org/10.24071/jpsc.004492

J. Pharm. Sci. Community, 2024, 21(1), 44-50

Article Info

Received: 25-03-2022
Revised: 05-09-2023
Accepted: 16-09-2023

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Keywords:
Antioxidant; DPPH; Effervescent; *Flavonoid; Oxalis dehradunensis* Raizada

ABSTRACT

Antioxidants and their health implications are widely studied related to their benefits in reducing free radical exposure. *Oxalis dehradunensis* Raizada is a type of wild mountain clover containing flavonoids and polyphenols. These contents allow the leaves to be consumed in a more practical, effective, and efficient way by processing the extract into effervescent granules. This experimental study used samples of *Oxalis dehradunensis* Raizada ethanol extract formulated in the form of effervescent granules. The content included citric acid, tartrate acid, lactose and sodium bicarbonate. The antioxidant activity assays were conducted by DPPH methods including testing the total phenol and flavonoid contents for the extracts and forms of effervescent granules. The total phenol content analysis used the Folin-Ciocalteu method while the total flavonoid content used the colorimetry method. The results identified the extract as the hygroscopic extract which had increasing IC_{50} for upgraded content of the formula but looked wet and was not stable. The experiment for the formula of effervescent granules was fulfilled by adding povidone, aspartame and polyethylene glycol. It required angle of repose which was 20^0-40^0 with a flow time not exceeding 10 seconds. The tap density also fulfilled the requirements, with the smaller the granule tap density, the greater the compression volume. The extract has a good antioxidant with IC_{50} value which reached near moderate to high levels. Although the formula 4 of effervescent granules was the best, it did not have the best antioxidant activity. Based on the results from the antioxidant activity assays, the extract has good antioxidant activity but it decreased when made into effervescent granules.

INTRODUCTION

Currently, usage of antioxidants as supplements or therapy is being developed to decrease people's exposure to free radical activities. Free radicals are very unstable, reactive and can attack vulnerable substances in the body. The dangers of free radicals highlight the emergence of diseases because of their important role in tissue damage and pathological processes. Free radicals can cause damage to cells and tissues, contributing to the progression of autoimmune diseases, degenerative diseases, atherosclerosis, coronary heart disease, stroke, cancer, kidney failure, and human ageing. As a preventive to progressive diseases, antioxidants are needed to protect the body from the attack of free radicals and reduce the negative effects. Antioxidants are compounds that can inactivate the development of molecules' oxidation reactions or neutralize free radicals (Mawarni *et al*., 2020; Pratama & Busman, 2020; Satriyani, 2021; Turangan *et al*., 2019).

Indonesia is known as a country in which 22.3% of people prefer traditional therapy using herbal medicine. Recently, there is a tendency to go "back to nature'. The government has shown support for these complementary and alternative medicines through suitable facilities and

regulations (Undang-Undang Republik Indonesia Nomor 13 Tahun 2010, 2010). Many people often consume various useful herbs to stay healthy but the benefits are sometimes only known by limited groups of people. Accordingly, the efficacy of some supplements needs to be proven scientifically and not just only communicated privately. Many herbs usually grow wild and not many people have used them for their benefits, including the *Oxalis dehradunensis* Raizada (R.) leaf, which is also called by the name *acem acem*.

Oxalis dehradunensis R. is a type of wild plant or weed which has other purposes for farmers as a hand wash and cleanser from dirt and pesticides. The leaf has a clover-like shape with small flowers. Generally, it grows wild around plants that contain an abundance of water. This plant also contains water, especially in the stems and roots. Based on previous studies, this plant is a type of mountain clover and contains secondary metabolites such as saponins, flavonoids, polyphenols, tannins, steroids, and triterpenoids. This mountain clover is included in the genus and species: *Oxalis dehradunensis* Raizada (R.) (Mahyuni, 2021; Mahyuni *et al*., 2022).

Oxalis dehradunensis R. leaves are also often consumed by farmers. The butterfly-shaped leaf can be eaten as a salad or mixed into food for a tangy sensation. Meanwhile, the fruit at the root area is often consumed directly because it is fresh and sweet. The flavonoid contents in the leaf can be assumed as antioxidants with secondary metabolites and can be consumed more practically as effervescent granules. This study aimed to determine the antioxidant activities in the effervescent granule formula based on 2, 2-diphenyl-1-picrylhydrazyl (DPPH) antioxidant activity assays and to know the total phenol and flavonoid contents as antioxidant indicators in the effervescent granule formulations.

METHODS

The materials used in the preparations begin with the ethanol extract of *Oxalis dehradunensis* R. leaves as a raw material for making effervescent granules. These leaves are obtained from agricultural areas as weeds and collected within a day to prevent decay to be immediately dried and ground as simplicia. The extraction was done by maceration using 70% ethanol solvent. These leaves have good secondary metabolites, one of which contains moderate levels of flavonoids and phenols. They also contain a high content of water, saponins and high glucose (Mahyuni *et al*., 2022). This extract is a new innovation and has never been tested in dry granules form.

This experimental study was conducted to formulate the ethanol extract of *Oxalis dehradunensis* R. leaves into effervescent granules and assay the antioxidant properties of the effervescent granules' preparations. In the experimental scenario, trials for the formulations of effervescent granules with *Oxalis dehradunensis* R. extract were adjusted according to the results of the formula formed until the utilization of this extract was achieved as a measurable effervescent granules preparation. The ethanol extract of *Oxalis dehradunensis* R. was then formulated into effervescent granules with a content of citric acid, tartrate acid, lactose and sodium bicarbonate as the main ingredients of the effervescent granules (Burhan *et al*., 2012; Forestryana *et al*., 2020; Simbolon *et al*., 2021). The evaluations conducted included the angle of repose, flow time, and tap density tests as a physical evaluation of effervescent granules preparations. The organoleptic test was conducted by looking at the color, smell, taste and the shape of the resulting granules (Rani *et al*., 2020).

The antioxidant assay of the ethanol extract of *Oxalis dehradunensis* R. effervescent granules also was done by using the DPPH assay method. Analysis of the antioxidant test using the DPPH method was conducted by looking at the color change of each sample after being incubated with DPPH. If all the DPPH electrons are paired with electrons in the extract sample, the color of the sample will change from dark purple to bright yellow (Tristantini *et al*., 2016). The analysis of total phenol contents was performed using the Folin-Ciocalteu method while the total flavonoid contents used the colorimetry method (Arnao, 2000; Molyneux, 2004).

RESULTS AND DISCUSSION

Nutritious plants often grow freely without people gaining much benefit from these plants, including the leaves of the wild plant, *Oxalis dehradunensis R.*, which is also known as mountain clover and contains secondary metabolites in the form of flavonoids that can act as antioxidants. Utilization of *Oxalis dehradunensis* R. can improve the public health, especially as an alternative in meeting the needs of maintaining healthy immunity through its antioxidant content by using the ethanol extracts of *Oxalis dehradunensis* R. in the form of effervescent granules.

The effervescent granules are a type of medical preparation which is very practical and was developed in the modern era. Effervescent content is from a special powder made in the form of granules and is usually added with two types of citric acid, tartrate acid and a base component (natrium bicarbonate). The acid and base components will react when the granules are mixed with water to release carbon dioxide in 2-3 minutes (Rani *et al*., 2020; Sihomning & Diana, 2019).

Formulation of effervescent granules as experiment scenario

The effervescent granules can also be used in food products as extracts of antioxidants to act as protection from free-radical exposure, one of which is the *Oxalis dehradunensis* R. leaf extract. The *Oxalis dehradunensis* R. ethanol extract has the characteristics of a very viscous green-brown liquid. This shows that the *Oxalis dehradunensis* plant has high water content. *Oxalis dehradunensis* extract is also one of the new extracts that has never been formulated in powder form. Initially, the effervescent granules formulation was done by mixing *Oxalis dehradunensis* viscous extract with citric acid, tartaric acid, lactose and sodium bicarbonate as a general effervescent mixture. However, this initial formulation failed since the base mixture did not dry completely.

Based on observations, since the *Oxalis dehradunensis* R. extract has a high water content, then in this formula, the lack of fillers affects the drying process of the effervescent powder mixture. In addition, there is no binder that can bind the mixture of acids and mixtures of bases so that the two mixtures do not mix properly.

In general, making effervescent granules is better if using the dry extracts. However, the highly aqueous *Oxalis dehradunensis* R. extract necessitated a change in the effervescent granule formulation. Due to the failure at the start of the formulation that prioritized four main ingredients, the research was changed to a wet granule formulation by adding polyvinyl pyrrolidone/povidone (PVP) as a binder in the effervescent granules formula (Yameela & Suprapto, 2016). Based on these characteristics, the experimental scenario in the research related to the effervescent granule formulation of *Oxalis dehradunensis* R. extract was reformulated and the antioxidant ability of the resulting effervescent granules could be measured and tested.

The experiment scenario in this research used four formulations of effervescent granules with *Oxalis dehradunensis* R. extract to find the best formula with antioxidant benefits (Table 1). As the first formulation, the effervescent granule formulation also requires additional mixtures such as PVP and aspartame to attach the ethanol extract of *Oxalis dehradunensis* R. with the effervescent granules.

In formula 1, physically, the effervescent granules are lumpy and cannot be sieved into effervescent granules as they should be. Additionally, the formula could not be continued because the yield of the formulation was very little and it was difficult to sift as a powder. To correct the failure of formula 1, the composition was increased but it turned out that the granule formula also could not be dried into granules, and instead turned into a caramel-like form.

Table 1. Formulation of effervescent granules with *Oxalis dehradunensis R.* leaf Extract

Formulation	F1	F2	F3	F4
Oxalis dehradunensis leaf extract	0.5 g	1.05 g	0,3 g	0.3 g
Citric acid	0.5 g	7 g	0.75g	0.75g
Tartrate acid	0.5 g	14 g	0.45 g	0.45 g
Lactose	2.4 g	28 g	6 g	6 g
Natrium bicarbonate	1 g	16.45 g	1g	1g
PVP	0.4 g	2.1 g	0.5 g	0.5 g
Aspartame	0.3 g	1.4 g	1 g	1 g
PEG	-	-	-	0.3 g

PEG, polyethylene glycol ; PVP, polyvinyl pyrrolidone/povidone.

Table 2. Results of angle of repose, flow time, and tap density of the effervescent granules formula

Effervescent Granules	F1	F2	F3	F4
Angle of repose	Not drying	Unfiltered	-	22.44^0
Flow time	Not drying	Unfiltered	11.2	3.3
Tap density	Not drying	Unfiltered	-	4.6%

Table 3. Antioxidant Activity Assay of Oxalis dehradunensis R. extracts with DPPH Assays.

Test solution	Regression equation	IC50 (ppm)	r-value
First iteration	Y= 0.4850 X + 1.0271	100.9647963	0.99527727
Second iteration	Y= 0.4844 X + 1.2971	100.5269587	0.99527081
Third iteration	Y= 0.4793 X + 1.2066	101.7896019	0.99643692

Table 4. The Total Flavonoid and Phenol for Each Formula

Effervescent granules	F1	F2	F3	F4
Total flavonoid	25.9641 mg/g GAE	26.2974 mg/g GAE	26.0923 mg/g GAE	27.0667 mg/g GAE
Total phenol	185.2222 mg/g GAE	170.7778 mg/g GAE	183.5556 mg/g GAE	191.8889 mg/g GAE

Figure 1. Effervescent granule formula 4.

We continued to change the ingredients and made formulas 2 and 3 which could ultimately produce effervescent granules. However, it was constrained by the calculation of flow time, angle of repose and tap index. Formula 3 could not meet the standards and could not be assessed; even after 45 minutes, the formula 3 showed a humid physical condition, based on the evaluation results of effervescent granule preparations.

After three trials in the experiment, we found that the extract is hydrophilic, and the formula was unstable as effervescent granules. Accordingly, it needed the PEG additive to be added as a lubricant and hygroscopic extract binder. PEG was added in formula 4 in order to make the effervescent formula become improved and fulfil the product stability test. With this purpose, 0.3 gr of PEG was added to make the formula stable as effervescent granules. The PEG provides a physical barrier to the reaction and as a lubricant, it can be used in effervescent granule formulations and is safe for consumption. The inherent hygroscopic nature of PEG could decrease the affinity for moisture of effervescent mixtures and provide a stabilizing effect (Apriliani e*t al.*, 2021; Jacob *et al.*, 2009; Wu *et al.*, 2022).

The best formula was formula 4 (Figure 1) which could met the required angle of repose which is 20^0-40^0 with a flow time not exceeding 10 seconds. The tap density also fulfilled the requirements, with the smaller the granule tap density, the greater the compression volume. The varied amount of the binding agent differed and therefore produced different granule shapes. The granule tap density from several formulas also varied but still fulfilled the required ≤20% (Voight, 1995). Although the results showed differences in each formula, overall, all of the effervescent granules fulfilled the needed requirements (Table 2).

Based on the results of the antioxidant assays, the effervescent granules in formula 4 are a better formula than the other formulas. The experiment of effervescent granules formulation which was conducted using the ethanol extract of *Oxalis dehradunensis* R. turned out to require further research related to the extract. The formulation process is difficult and different from other plant extracts such as oranges, dragon fruit or some types of leaf extracts. The formulation of the effervescent granules process used several additional ingredients which are dominated by lactose. The formulation process of effervescent granule preparations of ethanol extract of *Oxalis dehradunensis* R. needs to pay attention to the temperature factor to keep the preparations dry. This is emphasized because the

ethanol extract of *Oxalis dehradunensis* R. is hygroscopic and the preparation tends to become moist if it is not packed immediately in a closed package.

The tendency for the failure of the effervescent granule formulation of the ethanol extract of *Oxalis dehradunensis* R. can be assumed to be due to the wet nature of the extract and the ability of the extract to have high water content. The physical properties of a tablet or powder product are greatly influenced by the absorption or desorption of water during storage. In addition, the active ingredients having high humidity can cause problems with sticking to the die walls during tablet compression. Humidity that is above the humidity limit can also affect product stability and affect the manufacturing process of solid dosage formulations resulting in unfavorable tablet evaluation parameters (Pawar, Jaimini, Chauhan, & Sharma, 2014; Tomar, Singh, & Sinha, 2015).

Based on the results of the effervescent granules formulation, the extracted content shows that physically it contains a high content of water. The resulting ethanol extract of *Oxalis dehradunensis* R. was not a dry physical extract but classified as a wet extract with a specific smell. The effervescent granules formulation with extract *Oxalis dehradunensis* R. needs more drying process because the *Oxalis dehradunensis* properties contain water, so it is called a hygroscopic extract. This wet granule formulation method requires about 36 hours of drying, especially for alkaline mixtures. This leaf also has a fairly high glucose level so that when mixed with acid it can turn into caramel. As a result, it is necessary to pay attention to the formula size of the additive that supports the formation of good effervescent granules.

The antioxidant assay of ethanol extract of *Oxalis dehradunensis* R.

The DPPH test (Table 3) is the most appropriate method for assaying antioxidant compounds using organic solvents, especially alcohol solvents, namely ethanol. The IC_{50} results from the *Oxalis dehradunensis* R. leaf extract have good antioxidant abilities. With three times repetitions of the antioxidant test, the assays showed the extracted value of IC_{50} in concentrate of 101-150 ppm and is classified as a moderate category. The stable wavelength in the antioxidant testing with the DPPH methods showed strong absorption at 0.9856 a maximum wavelength of 515 nm in the DPPH assay as dark violet (Cao *et al*., 2020).

Differences in antioxidant activity can also be affected by the age of the leaves. This happens because different ages of the leaves showed there are differences in the concentration of secondary metabolites contained in these leaves. The more secondary metabolites contained, the stronger the antioxidant activity. This shows that the growth phase (plant age) affects the secondary metabolites which have compounds that have antioxidant activity (Ermayanti, Syafria, Harsojo, & Aryanti, 2012; Kuntorini, 2013).

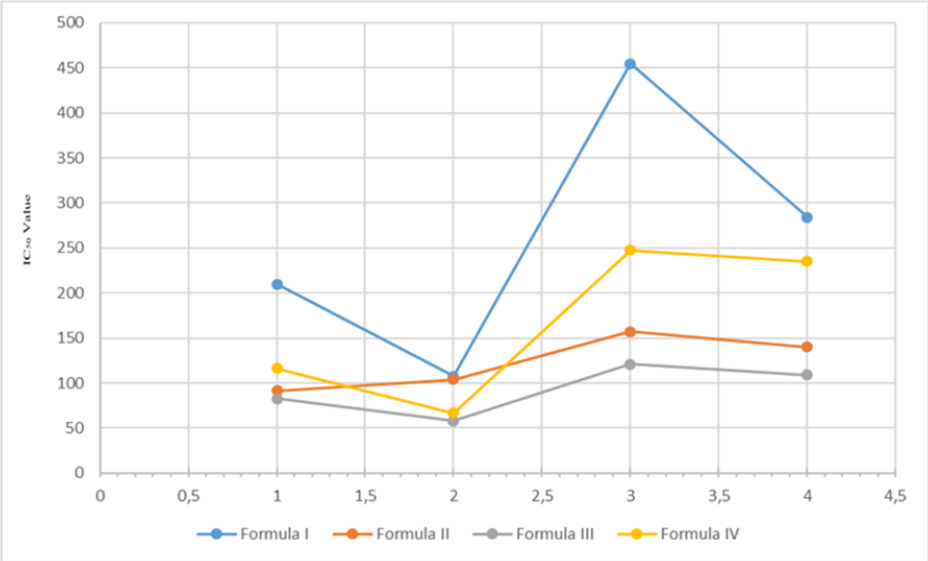

Figure 2. Extrapolation curve effervescent formula with IC_{50}.

Total Phenol and Flavonoid Contents

The total flavonoid and phenol for each formula was presented in Table 4. The total phenol content was higher than the flavonoids content because not all phenol contents in the extract were flavonoids. The existing phenols and flavonoids showed that the *Oxalis dehradunensis* R. leaf extract possesses antioxidant activity (Mukhriani *et al*., 2019). The extrapolation curve of the effervescent formula with IC_{50} can be seen in Figure 2.

The total flavonoid content in *Oxalis dehradunensis R.* extract was F4 27.0667 mg/g GAE, while the total phenol was F4 191.8889 mg/g GAE. The total phenol content was affected by the type of solvent. Phenol is a polar compound with the highest dilutable activity in the polar solvent. A polar solvent can dilute phenol better, so the extract has a higher content. The total phenol content was higher than the total flavonoid because not all phenols in the extract were flavonoid compounds. The existing phenols and flavonoids showed that the extract has antioxidant activity (Arif *et al.*, 2014; Rondonuwu *et al*., 2017; Wardhani *et al*., 2018).

CONCLUSIONS

The effervescent granules with *Oxalis dehradunensis R.* leaf extract had a good antioxidant level. The phenol and flavonoid contents showed that the extract had antioxidant activities. Based on the assays, the antioxidants of *Oxalis dehradunensis R* had moderate activity and also good availability to be formed into a plant medicine. However, it decreases when made into effervescent granules which is due to its hygroscopic properties. This research was conducted to further know the benefits of the effervescent granules that can be useful for reducing free radicals in the human body. As a source of sustenance for better immunity and health, it is also helpful and beneficial for workers including farmers, officers, chemical supervisors, etc.

ACKNOWLEDGEMENTS

We convey our gratitude to the Karo farmers' community who introduced *Oxalis dehradunensis R.* leaves to ensure the continuity of this study focusing on the benefits of *Oxalis dehradunensis R.* leaves. We also thank the staff of the *Laboratorium Fitokimia* Faculty of Pharmacy Universitas Sumatera Utara, who helped in the antioxidant testing. The study was also financially supported by RISTEK DIKTI BRIN with contract number 181/UN5.2.3.1/PPM/KP-DRPM/2021.

CONFLICT OF INTEREST

The authors have declared that no conflict of interest.

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