Characterization of Yellow Tabebuia Flower Extract (*Tabebuia Aurea*) Nanoparticles

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Abstract

Degenerative diseases can be prevented by natural antioxidants in plant. Yellow tabebuia flower is the natural antioxidants. Plant extracts can be developed into green synthesis nanoparticle to increase the effectiveness as medicinal materials. This research aims to determine the characteristics of yellow tabebuia flower extract nanoparticles and bioactivity as antioxidants. The methods included preparation and extraction of simplisia using ethanol solvent by maceration and sonication methods. The extract was determined flavonoid and phenol content by colorimetric method and antioxidant activity by DPPH method. The extract was also made into nano particles by ionic gelation method, with variations in the addition of tween 80 as much as 0.5, 0.75 and 1 ml. The results of this research are extract has a yield 13.09%, contains flavonoids, tannins, phenolics, alkaloids, saponins and terpenoids/steroids. The use of ionic gelation method can reducing particle size. Three formulas made the variation of surfactant addition has a particle size of 47-283 nm, in addition tween 80 1 ml has the smallest particle size of 47 nm with a zeta potential value of 39.3 mV.

Keywords: Tabebuia Aurea, Nanoparticles, Antioxidant Activity

1. INTRODUCTION

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In the current times, especially unhealthy lifestyles can cause degenerative diseases. According to WHO data up to 2018, degenerative diseases such as cancer, stroke, heart disease, diabetes may lead to death nearly 36 million people's. Estimates are that by 2030, there will be 52 million deaths caused these diseases (Riskesdas, 2018). To prevent these diseases, antioxidants are needed to neutralize the presence of free radicals. Source of antioxidants can be derived from synthetic antioxidants and natural antioxidants. Natural antioxidant compounds can be obtained from plants such as leaves, flowers and fruits (Purwanto et al., 2017). One of the plants that has potential as an antioxidant is yellow tabebuia *(Tabebuia aurea)*.

Tabebuia is one of the plants whose beautiful flowers can attract the attention of many people. So this plant is widely known as an ornamental plant because it has very beautiful flowers. In addition, yellow tabebuia *(Tabebuia aurea)* can be used in traditional medicine (El-Hawary et al., 2021). Tabebuia species are widely used in traditional medicine as antiinflammatory, treatment of malaria, skin infections, stomach disorders, anticancer, antibacterial, antifungal, snake venom neutralizer, and antidiabetic (Ferraz-Filha et al., 2017; Ferreira-Júnior et al., 2015; Malange et al., 2019; Paes et al., 2014; Sch, 2013).

Based on previous research, ethanol extract of yellow tabebuia bark contains phytochemical compounds such as flavonoid, alkaloid, tannin, terpenoid, steroid, phenolic and saponin (Sch, 2013; Sobiyana et al., 2019). Currently, many studies have been conducted on yellow tabebuia bark, but on the flower part is still not widely reported. This research were investigated about the content of phytochemical compounds and antioxidant activity from yellow tabebuia flowers.

Size and particle form is the factors that affect drug effectiveness. Particle size affects the solubility, absorption and distribution of the drug (Essien et al., 2022). One of the development technology to increase the effectiveness of drugs is *nanoparticle greensynthesis*. Biosynthesis methods (*green synthesis*) are being developed as an alternative to making nanoparticles, that are economical and eco-friendly compared to chemical and physical methods. Nanoparticle biosynthesis can carried out using plant extracts. Due to their diverse and complex composition, compounds contained in extracts such as alkaloids, flavonoids, saponins, steroids, terpenoids and tannins will act as reducing agents and stabilizers of nanoparticles (Bansal et al., 2020)

Nanoparticles that are often used as drug delivery and are not harmful to the body are chitosan nanoparticles (Putri et al., 2019). Chitosan is a natural polysaccharide that is non-toxic and biodegradable, besides that chitosan enable to form gels in an acidic atmosphere, chitosan also has properties as a matrix in drug delivery systems (D. Fitri et al., 2020; Khandbahale & Saudagar, 2017). One of the methods used for the synthesis of chitosan nanoparticles is the ionic gelation method (D. R. Fitri et al., 2021). This method is simple and easy to control (D. Fitri et al., 2020). The principle method is the electrostatic interaction between the amine group on positive charge chitosan and negative charge NaTPP polyanion forming a complexation between different charges, and the result chitosan nanoparticles to become more stable. Based on this description , the aim of this research to determine the characterization of yellow tabebuia flower extract nanoparticles and bioactivity as antioxidants.

2. METHODS

Materials and tools

The materials used in this research were yellow tabebuia flowers, 96% ethanol, Quercetin, Ethanol absolute, AlCl₃, Na₂CO₃, Asam galat, DPPH, DMSO, Natrium tripoliposfat, kitosan, tween 80. Chemicals for qualitative analysis, were distilled water, HCL p.a., dragendorff reagent, Mg powder, Lieberman-Buchard reagent, FeCl₃ p.a. Merck. The tools used were grinder, sieve, analytical balance, desiccator, vacuum pump, Buchner funnel, rotary evaporator, oven, vortex, spectrophotometer, particle size analyzer (PSA).

Preparation of Simplisia

Yellow tabebuia flowers derived from Malang, East Java, Indonesia. Flowers are washed with clean flowing water to remove dirt and dust. Fresh tabebuia flowers that have been cleaned are then dried in the sun covered with a black fabric cover until the flowers become easily crushed. Dried tabebuia flowers are then dry sorted and crushed using a grinder and sieved using a 60 mesh sieve.

Extraction

Simplisia 180 g was extracted with 1:8 ethanol solvent for 24 hours by using maceration method and then sonication for 35 minutes with a frequency of 40 KHz. Furthermore, the filtrate was evaporated using a rotary evaporator (Susanti et al., 2021).

Preparation Tabebuia Nanoextract

Yellow tabebuia flower extract 50 mg was dissolved in 0.5 mL of DMSO and add 15 ml 0.1% NATPP. The mixture of extract and NATPP was slowly poured into 45 mL 0.2% chitosan solution and stirred with a magnetic stirrer for 10 minutes. Next, 0.5 mL tween 80 was added and stirred using a magnetic stirrer for 20 minutes until all of the NATPP solution ran out and a nano particle suspension was formed (D. R. Fitri et al., 2021). This treatment also doing on two formulas with variations in the addition 0.75 and 1 ml tween 80.

Table 1. Tenow Tabebula Tiower Manoextract Torindia			
Formula	1	2	3
DMSO	0,5	0,5	0,5
Natrium tripolyposphate (NATPP) 0,1%	15	15	15
Chitosan 0,2%	45	45	45
Tween 80	0,5	0,75	1

Table 1. Yellow Tabebuia Flower Nanoextract Formula

Phytochemical Screening

Phytochemical screening is carried out by color reactions including flavonoids, alkaloids, saponins, tannins, phenolics, terpenoids / steroids, and essential oils (Shaikh & Patil, 2020)

3. RESULT AND DISCUSSION

Characteristics Tabebuia Flower Extract

The extraction process of tabebuia flowers was carried out by a combination of two extraction methods, maceration and followed by sonication. The purpose of combination method to get yield extract greater. Tabebuia flower ethanol extract 23.57 g produce a yield value of 13.09%. According by previous research, 60-minute sonication method produces a greater percentage yield than maceration method for 7 days. (Debiasi et al., 2021). So the

Characterization of Yellow Tabebuia Flower Extract (Tabebuia Aurea) Nanoparticles

combining extraction methods, will be produces a greater extract yield than using only one extraction method. The high yield results indicate that the chemical compounds that also can be extracted so quite large (Briones-Labarca et al., 2019).

Table 2. Yield and Extract Color			
No	Variable	Characteristics	
1	Yield	13,09%	
2	Color	Coklat gelap	
3	Consistency	Pasta	

Table 2 showed that the color of the extract is dark brown, because the flower samples when dried the color turn brown due to oxidation process. The consistency of the extract is pasta because the extract produced is very concentrated.

Extract Phytochemical Screening

The results show that the ethanol extract of tabebuia flowers contains all secondary metabolites (Table 3).

The secondary metabolites in tabebuia flower extract include phenolic compounds (flavonoids, tannins, and phenols), alkaloids, saponins, and triterpenoids. The phenolic compound has beneficial in health such as antioxidant, antimicrobial, anti-inflammatory, anticancer, antidiabetic and cardioprotective activities (Cosme et al., 2020)

No	Secondary Metabolites	Result Test	
1	Flavonoid	+	
2	Alkaloid	+	
3	Saponin	+	
4	Tanin/Phenol	+	
5	Triterpenoid/steroid	+	
6	Essential oil	-	
Not	Note: + (presence): - (absence)		

Table 3. Extract Phytochemical Screening

Note: + (presence); - (absence)

Flavonoids are the largest group of phenol compounds found in nature. These compounds are responsible for the red, purple, blue, and yellow colors in plants. (Teng & Chen, 2019). Flavonoids are natural phenolic compounds that have potential as antioxidants. Flavonoids are derivatives of 2-phenyl-benzyl-y-pyrone with biosynthesis using the phenylpropanoid pathway. Flavonoids act as antibacterial, anti-inflammatory, antioxidant and antidiabetic (Early Febrinda et al., 2013).

Alkaloids are the most common secondary metabolite compounds that have nitrogen, found in plant and animal tissues. In general, alkaloids have one or more nitrogen atoms with base character so they are called alkaloids. Alkaloids function to protect plants from disease, pest attacks, as development regulators, and as mineral bases to regulate ion balance in parts

of the plant included in the secondary metabolite group, the function of alkaloids as antibacterial, antibiotic and antiviral (Chiangnoon et al., 2022; Cushnie et al., 2014).

Saponins are a group of compounds with amphiphatic glycoside structures in a complex form consisting of steroids and triterpenoids. Saponins have biological activities such as maintain heart muscle, inhibit platelet aggregation, improve heart blood circulation, improve peripheral circulation, decrease cholesterol and blood triglycerides level. (Anwar & Hussain, 2017) also have hemolytic activity, antiinflammatory, antibacterial, antifungal, antivirus, anticancer and cytotoxic activity (Ashour et al., 2019). Plant steroid compounds are reported act as anti-inflammatory, decrease cholesterol level (Ogbe et al., 2015), antitumor, immunosupresif, hepatoprotective, antibacterial, sex hormone activity, antihelmintic and cardiotonic (Patel & Savjani, 2015).

Tabebuia Nanoextract

The process of making nanoextracts, the ionic gelation method is used by mixing chitosan polymers and sodium tripolyphosphate which will produce interactions between positive charges on the amino groups of chitosan with negative charges of tripolyphosphate to form colloids with sizes on a nanometer scale. The result of organoleptical nanoextract show in table 4.

Formula	Organoleptical		
Formula	Color	Texture	Odor
1	Yellow light	Liquid	Typical tabebuia flower
2	Yellow light	Liquid	Typical tabebuia flower
3	Yellow light	Liquid	Typical tabebuia flower

Table 4. Organoleptical Test Result of Tabebuia Flower Nanoextract

The results from the three formulas have the organoleptical standards, the solution looks clear and there is no sediment or phase separation.

The characteristics of yellow tabebuia flower extract nanoparticles can be seen from the size of the nanoparticles and the zeta potential value. Particle size can affect the release system of a drug both oral, parenteral, rectal and topical preparations. A decrease in particle size can increase the absorption rate and affect the dissolution process of the active substance. Tabebuia flower extract has a particle size of 2,386 μ m. From the extract was made into three formulas. The result of three formulas, the particle size and potential zeta value show in table 5.

Formula	Particle Size	Zeta Potential Value
1	0,283 µm	34,6 mV
2	0,246 µm	35,5 mV
3	0,047 μm	39,3 mV

Table 5. Particle Size and Zeta Potential Value Yellow Tabebuia Flower Nanoextract

From the three formulas, the smallest particle size was obtained in formula 3. Based on the results, particle size is influenced by the addition of surfactant. If more of surfactant added, the the particle size produced smaller. The result same with previous research with the addition of tween 80, the size of nanoparticles becomes smaller and the characteristics of emulgel preparations are getting better (Baskoro Sanaji et al., 2019). The addition of surfactants produces a uniform nanoparticle size that serves to minimize the occurrence of agglomeration between particles so that the nanoparticle formation process perfectly. The hydrophobic and hydrophile properties possessed by surfactants will maintain the final particle size so that the resulting nanoparticles are more stable (Ismayana et al., 2017).

Besides particle size, zeta potential is one of the most important characterizations of nanoparticles. The main reason for testing zeta potential is to predict the stability of colloidal solutions. Nanoparticles with zeta potential values smaller than -30 mV and larger than +30 mV have higher stability (Abdassah, 2017). In this research, the three formulas have zeta potential values above 30 mV. So it can be concluded that the nanoparticles formed from each formula have good stability.

5. CONCLUSION

Yellow tabebuia flowers extracted using 96% ethanol solvent has a yield value of 13.09%. The extract contained secondary metabolites of flavonoids, tannins, phenolics, alkaloids, saponins and terpenoids/steroids. The use of ionic gelation method in the preparation of nanoparticles proved effective in reducing particle size. Three formulas with the variation of surfactant addition has a particle size of 47-283 nm, in formula 3 has the smallest particle size of 47 nm with a zeta potential value of 39.3 mV. This shows that the particle size is also influenced by the addition of surfactant.

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BIBLIOGRAPHY

Abdassah, M. (2017). Nanopartikel dengan gelasi ionik. Jurnal Farmaka, 15(1), 45-52.

- Andriani, D., Murtisiwi, L. (2018). Penetapan Kadar Fenolik Total Ekstrak Etanol Bunga Telang (*Clitoria Ternatea L.*) Dengan Spektrofotometri Uv Vis. *Cendekia Journal of Pharmacy*, 2(1), 32–38. https://doi.org/10.31596/cjp.v2i1.15
- Anwar, Z., Hussain, F. (2017). Steroidal Saponins: An Overview of Medicinal Uses. *Ijcbs*, 11, 20–24. www.iscientific.org/Journal.html
- Aryal, S., et al. (2019). Total Phenolic content, Flavonoid content and antioxidant potential of wild vegetables from western Nepal. *Plants*, 8(4). https://doi.org/10.3390/plants8040096
- Ashour, A.S., et al. (2019). A review on saponins from medicinal plants: chemistry, isolation, and determination. *Journal of Nanomedicine Research*, 7(4), 282–288. https://doi.org/10.15406/jnmr.2019.07.00199
- Bansal, M., et al. (2020). Research Journal of Pharmaceutical, Biological and Chemical Sciences Green Synthesis of Gold and Silver Nanoparticles. 6(1710), 1710–1716.
- Briones-Labarca, V., Giovagnoli-Vicuña, C., Cañas-Sarazúa, R. (2019). Optimization of extraction yield, flavonoids and lycopene from tomato pulp by high hydrostatic pressure-assisted extraction. In *Food Chemistry* (Vol. 278). Elsevier Ltd. https://doi.org/10.1016/j.foodchem.2018.11.106
- Chiangnoon, R., Samee, W., Uttayarat, P., Jittachai, W., Ruksiriwanich, W., Sommano, S.R., Athikomkulchai, S., Chittasupho, C. (2022). Phytochemical Analysis, Antioxidant, and Wound Healing Activity of Pluchea indica L. (Less) Branch Extract Nanoparticles. *Molecules*, 27(3). https://doi.org/10.3390/molecules27030635
- Cosme, P., Rodríguez, A.B., Espino, J., Garrido, M. (2020). Plant phenolics: Bioavailability as a key determinant of their potential health-promoting applications. *Antioxidants*, 9(12), 1–20. https://doi.org/10.3390/antiox9121263
- Cushnie, T.P.T., Cushnie, B., Lamb, A.J. (2014). Alkaloids: An overview of their antibacterial, antibiotic-enhancing and antivirulence activities. *International Journal of Antimicrobial Agents*, 44(5), 377–386. https://doi.org/10.1016/j.ijantimicag.2014.06.001
- Debiasi, B.W., et al. (2021). Comparison between maceration and ultrasound-assisted extraction of white bracts with flowers of Bougainvillea spectabilis Willd. *Scientific Electronic Archives*, 14(2), 47. https://doi.org/10.36560/14220211297
- El-Hawary, S.S., Taher, M.A., Amin, E., AbouZid, S.F., Mohammed, R. (2021). Genus Tabebuia: A comprehensive review journey from past achievements to future perspectives. *Arabian Journal of Chemistry*, 14(4), 103046. https://doi.org/10.1016/j.arabjc.2021.103046
- Essien, E.R., Atasie, V.N., Nwude, D.O. (2022). Characterisation of ZnO nanoparticles prepared using aqueous leaf extracts of Chromolaena odorata (L.) and Manihot

esculenta (Crantz). In *South African Journal* scielo.org.za. http://www.scielo.org.za/scielo.php?pid=S0038-23532022000100014&script=sci_arttext&tlng=es

- Fathiah, F., Purwaningsih, I., Suryana, B. (2024). The Flavonoids, Phenolics, and Antioxidant Activity from Ethanol Extract of Fibraurea tinctoria Lour. *Jurnal Info Kesehatan*, 22(1), 114–123. https://doi.org/10.31965/infokes.vol22.iss1.1210
- Febrinda, A.E., Astawan, M., Wresdiyati, T., Yuliana, N.D. (2013). Kapasitas Antioksidan Dan Inhibitor Alfa Glukosidase Ekstrak Umbi Bawang Dayak. Jurnal Teknologi Dan Industri Pangan, 24(2), 161–167. https://doi.org/10.6066/jtip.2013.24.2.161
- Ferraz-Filha, Z. S., et al. (2017). Effects of the aqueous extract from Tabebuia roseoalba and phenolic acids on hyperuricemia and inflammation. *Evidence-Based Complementary* and Alternative Medicine, 2017. https://doi.org/10.1155/2017/2712108
- Ferreira-Júnior, J.C., et al. (2015). Isolation of a dihydrobenzofuran lignan, icariside E4, with an antinociceptive effect from Tabebuia roseo-alba (Ridley) Sandwith (Bignoniaceae) bark. Archives of Pharmacal Research, 38(6), 950–956. https://doi.org/10.1007/s12272-014-0468-4
- Fitri, D., Kiromah, N. Z. W., & Widiastuti, T. C. (2020). Formulasi Dan Karakterisasi Nanopartikel Ekstrak Etanol Daun Salam (Syzygium polyanthum) Pada Berbagai Variasi Komposisi Kitosan Dengan Metode Gelasi Ionik. JPSCR: Journal of Pharmaceutical Science and Clinical Research, 5(1), 61. https://doi.org/10.20961/jpscr.v5i1.39269
- Fitri, D.R., Syafei, D., Sari, C.P. (2021). Karakteristik Nanopartikel Ekstrak Etanol 70% Daun Jarak Pagar (Jatropha Curcas L.) dengan Metode Gelasi Ionik. *Jurnal Farmasi Higea*, 13(1), 1. https://doi.org/10.52689/higea.v13i1.324
- Irfansyah, F.D., Fatimah., Junairiah, J. (2024). SKRINING FITOKIMIA DAN AKTIVITAS ANTIOKSIDAN TIGA JENIS TABEBUYA (Tabebuia spp.). *Berita Biologi*, 23(1), 49–59. https://doi.org/10.55981/beritabiologi.2024.1668
- Ismayana, A., et al. (2017). Sintesis Nanosilika Dari Abu Ketel Industri Gula Dengan Metode Ultrasonikasi Dan Penambahan Surfaktan. *Jurnal Teknologi Industri Pertanian*, 27(2), 228–234. https://doi.org/10.24961/j.tek.ind.pert.2017.27.2.228
- Khandbahale, S.V., et al. (2017). Nanoparticle-A Review. Asian Journal of Research in *Pharmaceutical Science*, 7(3), 162. https://doi.org/10.5958/2231-5659.2017.00026.1
- Malange, K.F., et al. (2019). *Tabebuia Aurea* decreases hyperalgesia and neuronal injury induced by snake venom. *Journal of Ethnopharmacology*, 233(December 2018), 131–140. https://doi.org/10.1016/j.jep.2018.12.037
- Mohd-Zin, Z., Abdul-Hamid, A., Osman, A. (n.d.). *Antioxidative activity of extracts from Mengkudu (Morinda citrifolia L.) root, fruit and leaf.* www.elsevier.com/locate/foodchem
- Ogbe, R.J., et al. (2015). A Review of Dietary Phytosterols: Their occurences, metabolism and health benefits. A review on dietary phytosterols: Their occurrence, metabolism
- 22 ICHSN VOL. 1, NO. 1, 2024

and health benefits. *Pelagia Research Library Asian Journal of Plant Science and Research*, 5(4), 10–21. www.pelagiaresearchlibrary.com

- Paes, F., et al. (2014). *Tabebuia Aurea* decreases in fl ammatory, myotoxic and hemorrhagic activities induced by the venom of Bothrops neuwiedi. *Journal of Ethnopharmacology*, 1–6. https://doi.org/10.1016/j.jep.2014.10.045
- Patel, S.S., Savjani, J.K. (2015). Systematic review of plant steroids as potential antiinflammatory agents: Current status and future perspectives. *The Journal of Phytopharmacology*, 4(2), 121–125. https://doi.org/10.31254/phyto.2015.4212
- Purwanto, D., Bahri, S., Ridhay, A. (2017). UJI AKTIVITAS ANTIOKSIDAN EKSTRAK BUAH PURNAJIWA (Kopsia arborea Blume.) DENGAN BERBAGAI PELARUT. *Kovalen*, 3(1), 24. https://doi.org/10.22487/j24775398.2017.v3.i1.8230
- Putri, A.I., Sundaryono, A., Chandra, I.N. (2019). KARAKTERISASI NANOPARTIKEL KITOSAN EKSTRAK DAUN UBIJALAR (Ipomoea batatas L.) MENGGUNAKAN METODE GELASI IONIK. *Alotrop*, 2(2), 203–207. https://doi.org/10.33369/atp.v2i2.7561
- Rahman, M.M., et al. (2015). In vitro antioxidant and free radical scavenging activity of different parts of Tabebuia pallida growing in Bangladesh. BMC Research Notes, 8(1), 1–10. https://doi.org/10.1186/s13104-015-1618-6
- Riskesdas, K. (2018). Hasil Utama Riset Kesehata Dasar (RISKESDAS). Journal of Physics A: Mathematical and Theoretical, 44(8), 1–200. https://doi.org/10.1088/1751-8113/44/8/085201
- Sanaji, J.B., Krismala, M.S., Liananda, F.R. (2019). Pengaruh Konsentrasi Tween 80 Sebagai Surfaktan Terhadap Karakteristik Fisik Sediaan Nanoemulgel Ibuprofen. *IJMS-Indonesian Journal On Medical Science*, 6(2), 88–91.
- Santos-sánchez, N. F., & Salas-coronado, R. (2019). We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists TOP 1 % Antioxidant Compounds and. 1.
- Sch, K. (2013). Antioxidant Activity and Phytochemical Screening of Crude Endophytes Extracts of Tabebuia argentea Bur . &. 2013(August), 1641–1652.
- Shaikh, J.R., Patil, M. (2020). Qualitative tests for preliminary phytochemical screening: An overview. *International Journal of Chemical Studies*, 8(2), 603–608. https://doi.org/10.22271/chemi.2020.v8.i2i.8834
- Sobiyana, P., Manikandan, R., Anburaj, G. (2019). Comparative analysis of the in vitro antioxidant activity of Tabebuia rosea and Tabebuia argentea. ~ 2673 ~ Journal of *Pharmacognosy and Phytochemistry*, 8(1), 2673–2677.
- Susanti, F., et al. (2021). Pengaruh Variasi Waktu Sonikasi Terhadap Kadar Flavonoid Total Ekstrak Metanol Umbi Gadung (Dioscorea hispida Dennst.). *Prosiding Seminar Nasional UAD*, 1–10.
- Teng, H., Chen, L. (2019). Polyphenols and bioavailability: an update. Critical Reviews in
- 23 ICHSN VOL. 1, NO. 1, 2024

Food Science and Nutrition, 59(13), 2040–2051. https://doi.org/10.1080/10408398.2018.1437023

Yunita, Y., Santoso, A., Subandi, S. (2021). Xanthine oxidase inhibitory activity and identification of flavonoid in ethanol extract of sugar apple fruit (Annona squamosa L.). AIP Conference Proceedings, 2353(May). https://doi.org/10.1063/5.0052695