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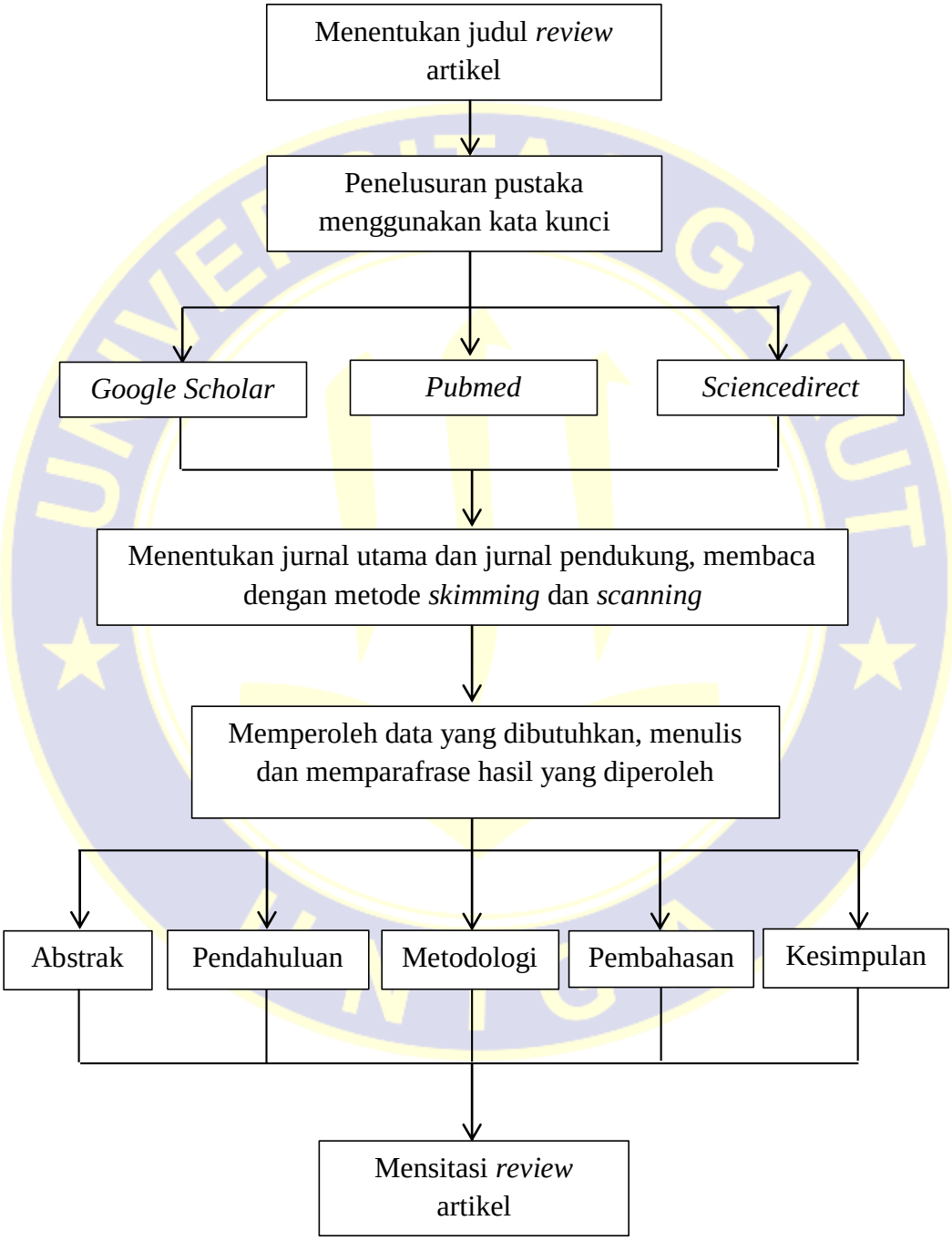
LAMPIRAN 1

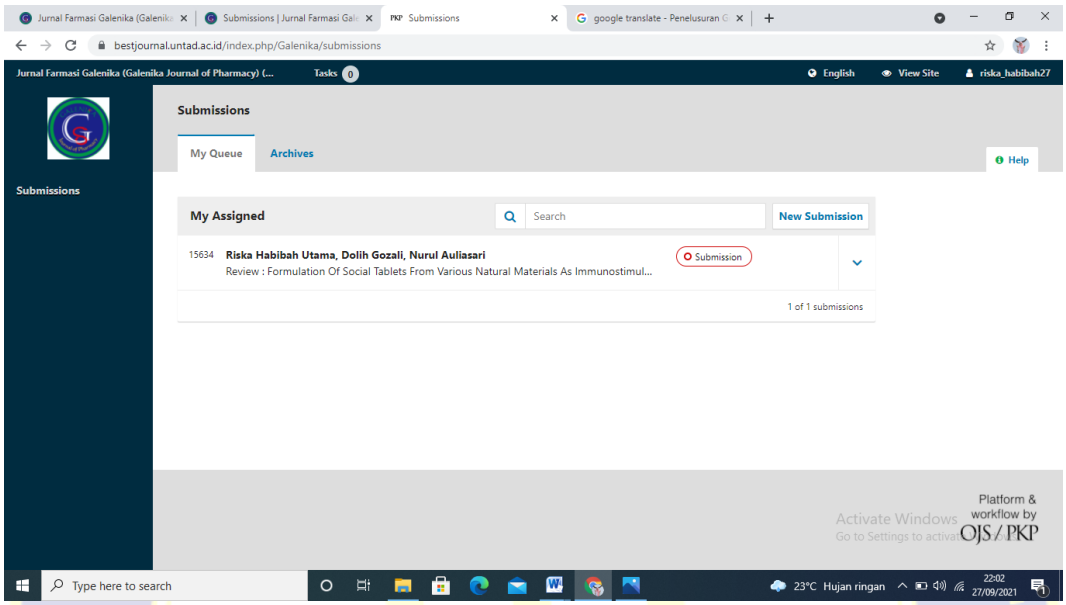
SKEMA PEMBUATAN *REVIEW* ARTIKEL



Gambar II.1 Skema metodologi penulisan *review* artikel.

LAMPIRAN 2

BUKTI SUBMIT *REVIEW* ARTIKEL



Gambar VI.2 Bukti submit *review* artikel

DAFTAR RIWAYAT HIDUP

DATA PRIBADI

Nama	: Riska Habibah Utama
Tempat/Tanggal Lahir	: Lampung, 27 Mei 1998
Jenis Kelamin	: Perempuan
Agama	: Islam
Warga Negara	: Indonesia
Status	: Mahasiswa
Alamat	: Kp. Karang Tengah Kel. Plawad Rt/Rw : 003/011 Kec. Karawang TImur Kab. Karawang
No. Telepon	: 089512284627
Email	: riskahabibah98@gmail.com

PENDIDIKAN

Formal

RA Muslimat Jakarta

SDN Plawad 1 Karawang

SMPN 2 Karawang Timur

SMK WIRASABA Karawang

Universitas Garut Prodi S1 Farmasi

Non Formal

PKL Apotek Kimia Farma Cikampek

PKL Rumah Sakit Proklamasi Rengasdengklok

PKL Apotek As-Syifa Garut

Kunjungan Indistri PT. Berkah Alam Nusantara

PENGALAMAN KERJA

Bekerja di Rumah Sakit Intan Sari Husada Kosambi Karawang

Bekerja di Apotek Kimia Farma Kosambi Karawang

PENGALAMAN ORGANISASI

Sekolah Dasar (SD)

- Praja Muda Karana (PRAMUKA) (Non Formal)

Sekolah Menengah Pertama (SMP)

- Palang Merah Remaja (PMR) (Non Formal)

Sekolah Menengah Kejuruan

- Rohani Islam (ROHIS) (Non Formal)
- OSIS sebagai Bendahara (Formal)

Universitas

- Lembaga Dakwah Kampus (LDK) (Formal)

  Sebagai Wakil Ketua (2018-2019)

- Badan Eksekutif Mahasiswa (BEM) (Formal)

  Sebagai Ketua Departemen Keagamaan (2019-2020)

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Review : Formulation Of Social Tablets From Various Natural Materials As Immunostimulants

Review : Formulasi Sediaan Tablet Hisap Dari Berbagai Bahan Alam Sebagai Imunostimulan

Riska Habibah Utama[1], Dolih Gozali[2], Nurul Auliasari[3]

[1,3]*Jurusan Farmasi, Fakultas Matematika dan Ilmu Pengetahuan Alam, Universitas Garut, Garut, Indonesia.*
[2]*Jurusan Farmasi, Fakultas Matematika dan Ilmu Pengetahuan Alam, Universitas Padjajaran, Bandung, Indonesia.*
[*]*E-mail: riskahabibah98@gmail.com*

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Corresponding Author:
Riska Habibah Utama
Jurusan Farmasi
Fakultas MIPA
Universitas Garut
Garut
44151
Indonesia
email: riskahabibah98@gmail.com

ABSTRACT

Background: The body defends itself from exposure to pathogenic microorganisms, one of which is the virus that causes COVID-19 through a modulation system. Increasing the body's immune response by giving compounds that have activity as immunostimulants. Indonesian regional plants have played so many roles during the COVID-19 pandemic. There are several Indonesian regional plants that can be used as immunomodulators in the prevention of COVID-19, namely black cumin (nigella sativa), tomatoes (lycopersicum esculentum Mill), mangosteen fruit (Garcinia mangostana L.). From various kinds of plants that have a bitter taste, it is necessary to make lozenges containing additional sweeteners to cover the unpleasant taste, so that the bitter taste of the plant can be covered. **Purpose:** This article review was made to determine the formulation of lozenges from various natural ingredients that best meets the requirements and has activity as an immunostimulant. **Methods:** Making this review article is a literature study, searching for sources or literature obtained in the form of reputable national and international journals published in the last 10 years published online. **Result:** The best formula is black cumin extract because it has a fairly high hardness, low friability and relatively faster disintegration time. The three natural ingredients, namely black cumin, tomatoes and mangosteen rind have been shown to have activity as immunostimulants.

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Keywords : Lozenges Formulation, Immunostimulant, Black Cumin, Tomatoes, Mangosteen Fruit.

ABSTRAK

Latar Belakang: Tubuh mempertahankan diri dari paparan mikroorganisme patogen salah satunya virus penyebab COVID-19 melalui sistem modulasi. Meningkatnya respon kekebalan tubuh yaitu dengan memberikan senyawa yang memiliki aktivitas sebagai imunostimulan. Tanaman daerah Indonesia begitu banyak memberi peran di masa pandemi COVID-19. Terdapat beberapa tanaman daerah indonesia yang bisa digunakan sebagai imunomodulator dalam pencegahan COVID-19 yaitu jintan hitam *(nigella sativa)*, buah tomat *(lycopersicum esculentum* Mill), buah manggis (*Garcinia Mangostana* L.). Dari berbagai macam tanaman memiliki rasa yang pahit maka untuk menutupi rasa yang tidak enak perlu dibuat sediaan tablet hisap yang mengandung bahan tambahan pemanis, sehingga rasa pahit dari tanaman tersebut dapat tertutupi. Tujuan: *Review* artikel ini dibuat untuk mengetahui formulasi sediaan tablet hisap dari berbagai bahan alam yang paling baik dan memenuhi persyaratan serta memiliki aktivitas sebagai imunostimulan. Metode: Pembuatan artikel *review* ini adalah studi pustaka, Pencarian sumber atau literatur yang diperoleh berupa jurnal nasional maupun jurnal internasional bereputasi terbitan 10 tahun terakhir yang diterbitkan secara *online*. Hasil: Formula paling baik adalah ekstrak jintan hitam karena memiliki kekerasan yang cukup tinggi, kerapuhan yang kecil serta waktu hancur yang relative lebih cepat. Ketiga bahan alam yaitu jintan hitam, buah tomat dan kulit buah manggis telah terbukti memiliki aktivitas sebagai imunostimulan.

Kata Kunci: Formulasi Tablet Hisap, Imunostimulan, Jintan Hitam, Buah Tomat, Buah Manggis.

INTRODUCTION

The COVID-19 outbreak spreads very quickly through human-to-human contact. According to Dewi et al (2020) the number of people exposed has increased drastically, so that it becomes one of the disturbing outbreaks. When providing treatment to people infected with this virus, it is not necessary during the recovery period, because of the self-medification nature of this virus, so it can be done when a person's immune system is strong. (Y. K. Dewi & Riyandari, 2020).

The body defends itself from exposure to pathogenic microorganisms, one of which is the virus that causes COVID-19 through a modulation system (Aziz et al., 2019). The body is composed of various kinds of organs that make up the organ system and the functional systems of the body from each of these organs work together in the integrity of the body system. In this system there is a body's defense system or commonly called the immune system (Activity et al., 2014). The immune system is a system that responds to an infection or foreign substance that enters the body where cells, proteins and chemical signals are involved. (Hidayah et al., 2020). This system is responsible for fighting pathogens that enter so that the body continues to function properly (Priyani, 2020). Increased immune response, namely by giving compounds that have activity as immunostimulants (Activity et al., 2014).

Immunostimulant is a substance that can increase the immune system naturally when various microorganism infections can be inhibited or combated. Immunostimulants can also cure diseases quickly because they are closely related to the immune system (Rosnizar. Kartini, E. Iskandar, 2015). A substance that functions to increase or increase the immune system so that it can have an effect, namely when consuming herbs that have efficacy as immunostimulants (Wulandari et al., 2019).

Indonesian regional plants have played so many roles during the COVID-19 pandemic. There are several Indonesian regional plants that can be used as immunomodulators in preventing COVID-19, namely black cumin seeds (Nigella sativa).(Y. R. Dewi et al., 2019), tomatoes (lycopersicum esculentum Mill) (Pujiastuti et al., 2019), mangosteen (Garcinia Mangostana L.) (Andriana & Chabib, n.d.). From various kinds of plants that have a bitter taste, it is necessary to make lozenges containing additional sweeteners to cover the unpleasant taste, so that the bitter taste of the plant can be covered. The concept of back to nature in utilizing materials derived from plants is increasingly in demand (Suparman & Saptarini, 2019). Compared to synthetic drugs, the use of traditional medicinal plants is cheaper and the side effects are relatively lower due to the variety of

plants that exist in Indonesia. (Hanum, 2018). One of the alternative choices is using herbal medicine as a dietary supplement. Dietary supplements are finished products as a complement to the nutrients consumed daily. Types of dietary supplements have various forms such as capsules, caplets, syrups, tablets (Rabbani et al., n.d.).

Traditionally, the use of medicinal plants from nature is done by boiling and boiling. However, this method is considered impractical if it is done every day, therefore to make it more practical and attractive, it is necessary to make pharmaceutical preparations in the form of lozenges (Yulianita, 2004). Lozenges are solid preparations consisting of one or more active substances, usually sweet-smelling and slowly soluble in the mouth. Lozenges have advantages such as regular tablet preparations, namely ease of production, practical packaging, storage, and transportation, then there is a guaranteed dose accuracy, practical use, compared to liquid oral preparations, lozenges are relatively more stable, compared to capsules. Lozenges are more stable and compared to parenteral preparations, lozenges are safer. Another advantage of lozenges is that they can cover the shortcomings of regular tablet preparations, such as for small children and certain people who have difficulty swallowing, lozenges are more practical to use because without swallowing, they only need to suck them in the mouth. (Sumber & Alami, 2018). Lozenges in terms of shape are preferred because of the sweetener used and for consumers who have difficulty swallowing, because they only need to suck it slowly, without using drinking water so that it becomes easier to use. (Hanum, 2018).

METHODS

The method used in making this review article is a literature study. The literature used is a research journal with the theme of formulation of lozenges from various natural ingredients as immunostimulants. Search sources or literature obtained in the form of reputable national journals and international journals published in the last 10 years published online through websites in the form of Google Scholar, Science Derect, Pub Med and others. The search was carried out using keywords such as “Formulation and Evaluation of Lozenges”, “Immunostimulants”, “Black Cumin”, “Tomatoes”, and “Mangosteen Fruit”. Furthermore, the determination of the journal that will be used as the main journal as the primary library, namely the journal that displays the formulation of lozenges from various natural ingredients as immunostimulants. So that 3 (three) main journals were obtained, namely journals regarding the formulation of lozenges from black cumin extract, Tomato juice extract and mangosteen rind extract and several other

journals, namely supporting journals that were used to support the literature from this review and other research findings journals. support data from major journals.

RESULT AND DISCUSSION

Based on the results of the literature search, information was obtained regarding the final formulation of lozenges, evaluation and immunostimulant activity of various natural ingredients including black cumin, tomatoes extract and mangosteen rind.

Tabel 1. Final Formulation of Lozenges

Plant Material	Ingredients	Function	Formula (mg)	References
Black Cumin	Black Seed Extract Dry	Active substance	75	(Y. R. Dewi et al., 2019)
	PVP	Fastener	37,5	
	Avicel PH 102	Fastener	112,5	
	Lactose	Filler	112,5	
	Starch 1500	Filler	37,5	
	Mg. Stearate	Fastener	22,5	
	Talkum	Lubricants	37,5	
	Aspartame	Glidant	3,75	
	Sucrose: Mannitol	Sweetener: Filler	1:5	
Tomatoes	Tomato juice powder	Active substance	20	(Pujiastuti et al., 2019)
	PVP K-30	fastener	5	
	Sodium benzoate	Preservative	0,2	
	Magnesium Stearate	fastener	1	
	Talkum	Lubricants	1	
	Sunset Yellow	Dye	0,01	
	Doxtrose	Sweetener	100	
Mangosteen Skin	Extract Powder	Active substance	380	(Andriana & Chabib, n.d.)
	Mannitol	Filler	952,8	
	Lactose	Filler	6,352	
	Acesulfame K	Sweetener	32	
	Gelatin (%)	Fastener	10	
	Mg. Stearate	Lubricants	7,814	

Dewi et al (2019) formulated lozenges of black cumin dry extract with a combination of sucrose-mannitol as a filler. By comparing 3 variations of sucrose concentration: different mannitol, namely 1:5, 1:6 and 1:7. Making lozenges of black cumin extract using PVP, Avicel PH 102, lactose, starch 1500, aspartame, sucrose and mannitol. The method used in the manufacture of black cumin extract lozenges is by using the wet granulation method. After evaluating the physical properties of the tablet including organoleptic observation, weight uniformity test, hardness test, friability test and tablet dissolving time

test, the black cumin extract lozenges with sucrose concentration: mannitol (1:5) obtained good characteristics as lozenges. namely from the tablet hardness test, dissolution time and friability.

Pujiastuti et al (2019) formulated a lozenge of tomato juice as an antidote to free radicals. By comparing PVP K-30 with different concentrations of 3 variations of binder, namely 1%, 2% and 3%. The ingredients in making tomato juice lozenges are tomato pollen, PVP K-30, sodium benzoate, magnesium stearate, talcum, sunset yellow and dextrose. The method in making lozenges of tomato juice extract was made using the wet granulation method. After evaluating the physical properties of the tablets including organoleptic, uniformity of tablet weight, uniformity of tablet size, tablet hardness, tablet friability, and tablet dissolving time of the three formulas, the result of the second formula was 2% which had the most optimal antioxidant activity.

Andriana et al (2014) formulated lozenges of mangosteen fruit extract with varying concentrations of gelatin as a binder. By comparing gelatin with different concentration variations, namely 2%, 4%, 6%, 8% and 10%. The ingredients in the manufacture of lozenges of mangosteen rind extract are extract powder, mannitol, lactose, acesulfame K, gelatin, stearic acid. The method in making lozenges of mangosteen rind extract was made using the wet granulation method. Based on the overall results of the tablet physical properties test including weight uniformity, size uniformity, friability and hardness, the best formula was obtained, namely the fifth formula with 10% gelatin concentration.

Tabel 2. Results of Evaluation of the Preparation of Lozenges

Natural Ingredients	**Evaluation**				**References**
	Weight uniformity	**Hardness (kg)**	**Fragility**	**Destroy Time (minutes)**	
Black Cumin	0,77	8,57	0,12 %	13,27	(Y. R. Dewi et al., 2019)
Tomatoes	0,20	9,39	0,63%	5,29	(Pujiastuti et al., 2019)
Mangosteen Skin	2,05	12,35	0,50%	13,62	(Andriana & Chabib, n.d.)
Condition		7-15 kg	<1 %	<30 minute	

Evaluation of the physical properties of lozenges included weight uniformity test, hardness test, friability test, disintegration time test and lozenge preference test. A good

lozenge has a hardness between 7-15 kg, a friability of not more than 1% and a tablet disintegration time of no more than 30 minutes in accordance with the requirements set by Pharmacopoeia Edition IV (Andriana & Chabib, n.d.).

The results of the evaluation of the weight uniformity test conducted by Dewi et al (2019) reported that none of the tablets weighed more than 5% and 10% of the average weight, it was proven that the black cumin extract lozenges had good weight uniformity. and has met the requirements set by Pharmacopoeia Edition IV. In a study conducted by Pujiastuti et al (2019), it was reported that the tomato pollen lozenges in the three formulas met the requirements. Weight uniformity is influenced by the results of the flow properties of the granules. The stable flow rate of the granules is influenced by the good flow properties of the granules, so that the number of granules that flows into the printing chamber, the shape obtained can be uniform when the printing process on the tablet press machine. Meanwhile, the research conducted by Andriana et al (2014) reported that increasing the concentration of gelatin produces granules with strong inter-particle bonds, so that the granules can easily fill the printing space of a tablet machine (punch).

The results of the tablet hardness test evaluation based on the data obtained (Dewi et al, 2019; Pujiastuti et al, 2019; Andriana et al, 2014) were black cumin of 8.57; tomato fruit is 9.39 and mangosteen rind is 12.35. Judging from the data, the tablet hardness test has met the requirements, in accordance with the provisions for the hardness of lozenges between 7-15 kg. The addition of mannitol can affect tablet hardness. In addition, judging from the nature of the extract used in lozenges, black cumin extract has moist properties (Y. R. Dewi et al., 2019). The higher the PVP K-30 content, the higher the tablet hardness will be. The influence of tablet hardness is by the nature of the material being compressed, the compression pressure is large and the amount and type of binder used (Pujiastuti et al., 2019). The addition of a higher gelatin binder results in the formation of stronger bonds between particles, so that when the granules are compressed into tablet form, the resulting tablet hardness is high when subjected to shocks (Andriana & Chabib, n.d.)

The results of the evaluation of the tablet friability test based on data obtained from research (Dewi et al, 2019; Pujiastuti et al, 2019 and Andriana et al, 2014) namely black cumin by 0.12%, tomatoes by 0.63% and mangosteen peel by 0, 50%. Judging from the data, the tablet friability test has met the requirements in accordance with the provisions

of the Indonesian Pharmacopoeia, the friability of lozenges is less than 1%. The higher the use of mannitol, the lower the friability of the tablet (Y. R. Dewi et al., 2019). Mannitol has hygroscopic properties, so the resulting tablet is more moist (Haryanti et al., 2012). The greater the addition of PVP K-30 binder, the smaller the friability value of the tomato pollen lozenges produced (Pujiastuti et al., 2019). The use of gelatin binders resulted in the formation of stronger interparticle bonds which resulted in tablets with high hardness and not easily brittle when there was a shock to the tablet (Andriana & Chabib, n.d.). The fragility of the tablet is strongly influenced by the hardness of the tablet, the lower the tablet hardness, the lower the bond between the constituent particles so that the level of brittleness is likely to be greater (Wikantyasning, 2011)

The results of the evaluation of the tablet disintegration time test were based on data obtained from (Dewi et al, 2019; Pujiastuti et al, 2019, 2011; Andriana et al, 2014) black cumin for 13.27 minutes, tomatoes for 5.29 minutes and mangosteen peel extract for 13. ,62 minutes. Judging from the data, the tablet disintegration time test has met the requirements, according to the provisions for a tablet disintegration time of less than 30 minutes (Andriana & Chabib, n.d.) (Y. R. Dewi et al., 2019). Tablet dissolving time is the time required for the tablet to dissolve or disintegrate into its constituent particles upon contact with a liquid. In order for the tablet to dissolve in the mouth, the tablet undergoes a disintegration process (breakdown of tablets into granules) and a deaggregation process (breakdown of granules into tablet constituent particles) (Wikantyasning, 2011). The addition of PVP K-30 binder content affects the dissolution time of lozenges, the higher the PVP K-30 binder content, the longer it takes for the tablet to dissolve in the mouth (Pujiastuti et al., 2019). The addition of a higher gelatin binder in the formulation carried out by Andriana et al (2014) resulted in lozenges with higher hardness. Thus, the dissolving time of lozenges becomes longer. The increase in the concentration of the binder causes the pores of the granules to become more compressed and the bonds between the particles are getting stronger, the harder the tablet is, the longer the tablet dissolving time (Wikantyasning, 2011). The dissolving time of tablets is not only seen from the concentration of the binder, but also depends on the saliva content of a person. (Andriana & Chabib, n.d.)

IMMUNOSTIMULANT ACTIVITY

Black Cumin. One of the natural ingredients used as disease prevention is black cumin extract (Nigella sativa). The black cumin plant has the most dominant chemical content, namely thymoquinone compounds which have various functions, one of which is as a hepatoprotector. The main component of black cumin has the ability to prevent the formation of nucleic acid (RNA) and protein synthesis from V. alginolyticus. This has been proven in the research that has been done by Fauzi et al (2014) that the administration of black cumin 7.5% is able to increase the immunity of white snapper infected with Vibrio alginolyticus there is less damage to organ tissue than without black cumin (ahmad fauzy, tarsim, 2014)

In research that has been done by Novisa et al (2015) black cumin is able to increase immunity in fish which can prevent VNN infection. Giving black cumin of 25 g in 1 kg of feed is able to inhibit the occurrence of tissue damage caused by VNN . infection (ahmad fauzy, tarsim, 2014).

The results of another study conducted by Juliana et al (2016) that giving black cumin can increase the survival of fish larvae which can improve the body's immune system. The best black cumin that can increase the survival of fish larvae is at a dose of 0.2 mg/gr of feed (Juliana & Agusnimar, 2016).

Tomato Fruit. Tomatoes contain lycopene compounds which act as immunostimulants. Lycopene is a carotenoid compound that is fat soluble, can be synthesized by plants and some microorganisms, but cannot be synthesized in animals and humans. According to the report of Iswari (2013) that tomato extract is one of the compounds that functions as an immunomodulator. Compounds contained in tomatoes are related to immunity against infectious diseases, including Plasmodium infection. In addition, based on the results of research conducted by Iswari (2013) reported in research quotes Iswari and Susanti (2012) that research on male Swiss strain mice that were given tomato extract and infected with Plasmodium berghei showed immunostimulant activity. The most effective dose in increasing the body's immune system to reduce and even kill parasites in the body is the administration of tomato extract at a dose of 10 mg/kgBW/day (Iswari, 2013)

Mangosteen Peel. Mangosteen rind contains xantone compounds which are quite strong as antioxidants, antiproliferative and antimicrobial. Xanthones have pharmacological

activity as antibacterial, antiplatelet aggregation, anti-inflammatory, antifungal, antileukemic, besides that xanthones can stimulate the central nervous system. Based on research that has been done by Budi, S & Sabriani (2012) reported that mangosteen peel extract can be used as an immunostimulant as a substitute for antibiotics in the control of vibrosis which is shown to have a very strong inhibition zone against Vibrio Harveyii bacteria in hatchery activities (Sabriani, 2012)

Based on research Nurwaini et al (2011) reported that the extraction of active compounds from basil leaves is one way so that the substances and properties contained in basil leaves can be maintained for a longer or stable time. So that the extracts from natural ingredients including black cumin extract, juice extract for tomatoes and mangosteen rind extract are very suitable to be formulated in lozenges.

CONCLUSION

Based on the results of a review of several journal articles that have been reviewed, it can be concluded that the three formulations of lozenges from natural ingredients have met the requirements for good physical properties of lozenges. Judging from the results of the final evaluation of the three formulas, it is known that the best formula is black cumin extract because it has a fairly high hardness, small friability and relatively faster disintegration time. The three natural ingredients, namely black cumin, tomatoes and mangosteen rind have been shown to have immunostimulant activity.

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