CHAPTER 2
LITERATURE REVIEW

Acne vulgaris is the most prevalent skin disorder and has been estimated to affect at least 80% of the population between the ages of 12 and 25. Although acne may begin in pre-adolescence when adrenal androgens begin to stimulate the sebaceous gland but it is most commonly seen during adolescence when both the adrenals and gonads provide androgen stimulation of sebocytes. Increasingly, acne can be found in adults, particularly in women during the third to fifth decades of life. The pathogenesis of acne is clearly multifactorial, involving four principal factors that help to explain the wide variation in clinical manifestation.

1. Altered follicular epithelial differentiation leading to hyperproliferation and abnormal desquamation, resulting in the precursor lesion of all other acne lesions, the microcomedo.
2. Increased sebum production.
3. Proliferation of *Pionibacterium acnes* and *Staphylococcus aureus*
4. Inflammation resulting from pro-imflammatory cytokines produced by *P.acnes* and possibly from free fatty acids generated by the hydrolysis of sebum triglycerides by lipase secreted by *P.acnes*. Follicular rupture may lead to more intense and chronic inflammation. [5]

2.1 Causes of acne [5]

Acne develops as a result of blockages in follicles. Hyperkeratinization and formation of a plug of keratin and sebum (a microcomedone) is the earliest change. Enlargement of sebaceous glands and an increase in sebum production occur with increased androgen production at adrenal gland. The microcomedone may enlarge to form an open comedone (blackhead) or closed comedone (whitehead). Whiteheads are the direct result of skin pores becoming clogged with sebum, a naturally occurring oil, and dead skin cells. In these conditions the naturally occurring largely

commensal bacteria *Propionibacterium acnes* and *Staphylococcus aureus* can cause inflammation, leading to inflammatory lesions (papules, infected pustules, or nodules) in the dermis around the micromedo or comedo, which results in redness and may result in scarring or hyperpigmentation.

Pathophysiology of acne [8]

Comedogenesis and acnegenesis are actually discrete processes, but they are usually associated with one another, with the latter often succeeding the former. Information of the follicular epithelium, which loosens hyperkeratotic material within the follicle creating pustules and papules, characterizes acnegenesis. Comedogenesis is best described as a noninflammatory follicular reaction manifested by a dense compact hyperkeratosis. Because the etiology of such lesions varies from person to person and within individuals, it is difficult to categorically identify or isolate a basic cause of acne, however, three principle factors have been identified. The primary causal factors in acne work interdependently and are mediated by such important influences as heredity and hormonal activity.

Sebaceous gland hyperactivity [8]

Sebum is continuously synthesized by the sebaceous glands and secreted to the skin surface through the hair follicle pore. The excretion of lipids by the sebaceous glands is controlled hormonally. The sebaceous glands are located all over the body but are largest and most numerous in the face, back, chest, and shoulders. These glands become more active during puberty because of the increase in androgens, particularly testosterone, which spurs sebum production. This imbalance between sebum production and the secretion capacity leads to a blockage of sebum in the hair follicle followed by inflammation.

Hormones continue to affect sebaceous gland activity into adulthood. In males, lipid secretion is regulated by the action of testosterone. In females, the immediate increase in luteinizing hormone following ovulation incites acceleration in sebaceous gland activity. The higher sebum secretion then stimulates or exacerbates acne breakouts usually 2 to 7 days prior to menstruation. Women experiencing excessive androgen states, such as those seen in polycystic ovarian disease, frequently suffer from acne as well.

The literature reveals no discernible differences in the sebum composition of acne patients as compared to age-matched controls. Strauss and Thiboutot [2] have noted, though, an inverse relationship between sebum secretion and linoleic acid concentration in the sebum of acne patients-the higher the sebum secretion, the lower the linoleic acid concentration.

Changes in follicular keratinegative charges, keratinization [8]

In the lower portion of the follicular infundibulum, the normal process of keratinization occurs in the same way that it occurs on the skin's surface. This maturing of keratinocytes and subsequent exfoliation into the follicle marks the beginning of the formation of comedones. In acne patients, these keratinocytes tend to stick together because of the effects of positive and negative charges, the actions of transglutaminase, and the stickiness of sebum. The clumped keratinocytes block the pore/follicle, creating a blackhead if the pore is open ("open comedone") or a whitehead if it is closed ("closed comedone"). The clogged pore is a great nutritional source for bacteria so *Propionibacterium acnes* gravitate to the blocked pores. The immune system recognized the presence of bacteria and mounts an immune response resulting in redness, pus, as well as inflammation, and the typical "pimple" results. Most of the inflammation, however, is likely due to inflammatory mediators that are released when bacteria digest sebum.

Primary cause

The root causes of why some people get acne and some do not fully known. It is known to partly heredinary. Several factors are known to be linked to acne:

- Family/Genetic history. The tendency to develop acne runs in families. For example school-age boys with acnes often have other member in their family with acne as well. A family history of acne is associated with an earlier occurrence of acne and an increased number of retentional acne lesions.

- Hormonal activity, such as menstrual cycles and puberty. During puberty , an increase in male sex hormones called androgens cause the follicular glands to get larger and make more sebum.

- Inflammation, skin irritation or scratching of any sort will activate inflammation. Anti-inflammatories are know to inprove acne.

- Stress, through increased output of hormones from the adrenal glands. While the connection between acne and stress has been debated, scientific research indicates that “increased acne severity is significantly associated with increased stress level.” The National Institutes of Health list stress as a factor that “can cause an acne flare”. A study of adolescents in Singapore observed a statistically significant positive correlation between stress levels and severity of acne.

- Hyperactive sebaceous glands, secondary to the thres hormone source above.

- Accumulation of dead skin cells that block or cover pores.

- Bacteria in the pores. *Propionibacterium acnes* (*P.acnes*) is the anaerobic bacterium that causes acne. In vitro resistance of *P.acnes* to commonly used antibiotics has been increasing.

- Any medication containing lithium, barbiturates, anabolic steroids or androgens, chronic use of amphetamines or other similar drug.

2.1.1 Diet [6]

Chocolate

The popular belief that consumption of chocolate can cause acne is not supported by scientific studies. As discussed below, various studies point not to chocolate, but to the high glycemic nature of certain foods containing simple carbohydrates as a cause of acne. Chocolate itself has a low glycemic index. Chocolate is also high in antioxidant, and since chocolate boots the serotonin levels in the brain, it may reduce stress and actually aid in restraining acne.

Milk

Recently, three epidemiological studies from the same group of scientists found an association between acne and consumption of partially skimmed milk, instant breakfast drink, sherbet, cottage and cream cheese. The researchers hypothesize that the association may be caused by hormones (such as several sex hormones and bovine insuin-like growth factor (IGF-1) or even iodine present in cow milk.

Carbohydrates

The long-held belief that there is no link between diets high in refined sugars and processed foods, and acne, has recently been challenged. The previous belief was based on earlier studies (some using chocolate and Coca Cola) that were methodologically flawed. Three recent low glycemic-load hypothesis postulates that rapidly digested carbohydrates foods (such as soft drink, drink, sweets, white bread) produce an overload in blood glucose (hyperglycemia) that stimulates the secretion of insulin, which in turn triggers the release of IGF-1. IGF-1 has direct effects on the pilosebaceous unit (and insulin at high concentrations can also bind to the IGF-1 receptor) and has been shown to stimulate hyperkeratosis and epidermal hyperplasia. These events facilitate acne formation. Sugar consumption might also influence the activity of androgens via a decrease in sex hormone-binding globulin concentration.

Vitamins A and E

Studies have shown that newly diagnosed acne patients tend to have lower levels of vitamin A circulating in their bloodstream than who are acne free. In addition people with severe acne also tend to have lower blood levels of vitamin E.

2.1.2 Hygiene [6]

Acne is not caused by dirt. This misconception propably comes from the fact that blackheads look like dirt stuck in the opening of pores. The black color is not dirt but simply oxidized keratin. In fact, the blockages of keratin that cause acne occur deep within the narrow follicle channel, where it is impossible to wash them away. These plugs are formed by the failure of the cells lining the duct to separate and flow to the surface in the sebum created there by the body. Built-up oil of the skin can block the passages of these pores, so standard washing of the face could wash off old oil and help unblock the pores.

2.1.3 Cosmetics

Comedogenic agents such as heavy oil, greases or dyes in cosmetic cream and hair sprays can exacerbate acne. Patients who use cosmetics should be advised to use water-based products instead of occlusive, oil-based products.

2.2 Treatments of acnes [10,21]

There are various products available for the treatment of acnes, many of them are without any scientifically proven effects. Many treatments that promise big improvements within two weeks are likely to be largely disappointing. A combination of treatments can greatly reduce the amount and severity of acne in many cases. Those treatments that are most effective tend to have greater potential for side effects and need a greater degree of monitoring, so a step-wise approach is often taken. Besides adding expense with little benefit, complex regimens are usually more irritating and present problems with compliance.

2.2.1 Topical medications [10]

Tretinoin (Retin-A) is available in a variety of bases, and is the most active agent available for treatment of comedones. It acts by increasing the rate of cell turnover and loosening the impacted keratinous plugs. In addition, it increases the permeability of the skin to other medication. The drug does, however, increases the potential toxicity from sun exposure. Use in the summer months must be carefully

consider and combination with sunscreens is wise. Tretinoin is especially irritating to redheads, blondes, and those with blue eyes.

Initial use is with Retin-A Cream 0.05-0.1% nightly. After the patient tolerates this without excessive scaling or peeling, if necessary twice daily use is allowed. Retin-A Gel 0.01-0.025% or lotion 0.05% may be used for more advanced lesions but is more irritating. After 4-6 weeks use, a slight flare of disease activity is expected. Retin-A works principally on comedonal acne.

Benzoyl peroxides are available as washes (Desquam X Wash, Benzac Wash) or as 2.5%, 5% and 10% gels or lotions. These medicines function best when they are able to penetrate the comedones and liberate oxygen into the sebaceous duct. *P.acnes* is an obligate anaerobe and is destroyed by this lotion. This Treatment can be used in both comedonal and inflammatory acne. Their activity is synergistic when combined with Retin-A, tretinoin allows the benzoyl peroxide to penetrate more deeply. When used together with Retin-A it is advisable to begin one medicine first and after the skin "hardens" to its effect, the other is added. A typical regimen is a benzoyl peroxide in the morning and Retin-A nightly. If the combined daily use is too irritating, altermate nightly applications are usually well tolerated.

The different bases allow use on different types of skin. Desquam-X Cream is the most drying and is used on oily skin. Benzac W 10 is the least drying and is used on the most sensitive skin. Persa-Gel is between the two in irritancy. Caution must be exercised in using these medicines on the chest and back since there is the potential for staining the clothes. All medicines are applied 10-15 minutes after washing and rubbed in well.

2.2.2 Oral antibiotics [10] Currently, tetracycline is the antibiotic that most widely used for acne therapy. Other medications used are erythromycin, clindamycin, and infrequently,trimethoprim/sulfamethoxazole (Bactrim, Septra).

Tetracycline is used in cases of inflammatory acne. It is given on an empty stomach. Most dermatologists suggest taking it 2 hours after or 0.5-1 hour before a meal. A typical starting dose is 1 gm daily in divided doses. In severe acne a maximum dose of 2 gm daily is allowed. It is usually necessary to continue 1 gm daily for 1-2 months. After a reasonable period of time at this dose, gradual tapering

is begun. At a level of 250 mg/day tetracycline is able to inhibit free fatty acids. Flares frequently occur within 1 month after the drug is withdrawn alternate day or intermittent therapy is well tolerated in these cases. It is also frequently necessary to allow woman 250-500 mg/day for the 1 week prior to menses. Children and pregnant woman should not take tetracycline. Woman, especially those using birth-control pills, are best advised of the possibility of precipitating a yeast infection.

Doxycycline and minocycline are alternatives to therapy with tetracycline. They are more expensive and have increased risk of phototoxicity. Their use is indicated only for stubborn cases.

Erythromycin is used for in the same doses as tetracycline, and seems to be about as effective. Some erythromycins may be given with food. There seems to be an unending supply of newer erythromycin formulation none is demonstrably superior to the others.

Clindamycin is used for very resistant acne. This is a potent drug and has very limited used it must be discontinued with any signs of GI intolerance. At a dose of 75 mg, bid to tid it exerts marked anti-acne effect.

Trimethoprim/sulfamethoxazole (Bactrim-DS, Septra-DS) in a dose of 1 tablet bid has been suggested to be of some benefit. Its use should not be routine until long-term studies indicate its efficacy and lack of toxicity.

Dapsone is another adjuvant therapy. Its use is combined with an oral antibiotic and continuous topical therapy. A dose of 100 mg/day is effective in suppressing inflammatory elements in some resistant or severe cases. It is not used in comedonal acne. After several months, the dose is slowly tapered, and then, if possible, discontinued. Appropriate laboratory studies include G6PD determination and CBC at increasing intervals thereafter.

Gram-negative folliculitis may occur aside from the usual complications induced by antibiotics (nausea, vomiting, epigastric distress, vaginal yeast infection, and diarrhea). This complication is usually present in somewhat older patients receiving long-term broad-spectrum antibiotics. It appears as either superficial pustules about the nose or less commonly as deep-seated cysts and nodules. The causative gram-negative bactaria usually originate in the nose. Treatment is usually an antibiotic such as ampicillin in doses of 250 mg, qid for 7-14

days, with tapering thereafter. Prolonged therapy is often needed. A topical antibiotic applied to the anterior nares is frequently helpful.

2.2.3 Topical antibiotics [10] have recently gained much popularity in many cases they are as potent as oral antibiotics in the usual doses. It appears that commercially prepared vehicles (Vehicle N) are better carriers and penetrate more deeply than home-concocted vehicles such as isopropyl alcohol, water, and propylene glycol. The efficacy of these commercial products combined with antibiotics is also much more impressive than compounded preparations. At twice daily use a significant reduction in papule and pustule count within 2 weeks is evident. Improvement continues with use up to 12-16 weeks. Approximately 50-60% improvement in the inflammatory elements is seen while there is only minimal resolution of the comedonal elements.

2.2.4 13-cis-retinoic acid (Accutane) [10] is an excellent drug that signify-cantly decreases the sebaceous secretion rate in less than 1 month and may well lead to clearing of severe resistant or conglobate acne. 100% of those using this therapeutic agent will have some adverse reaction. The current dosage recommendation are 1-2 mg/day. Lesions on the face are more responsive than torso lesions, and improvement may be maximal after discontinuation of therapy after 12-20 weeks of use. Adverse reactions include cheilltis, facial dermatitis/eczema, desquamation, dry nasal mucosa, pruritus, and conjunctivitis. Some have hair loss, arthralgias, as well as an elevation in liver enzymes and triglycerides. This is not a routine treatment and is not uniformly successful. It should be reserved for unresponsive cystic acne.

2.2.5 Vitamin A [10] is probably placebo therapy in the normally-used doses of 25,000-50,000 or even 100,000 units/day. For those patients who want a “pill” but who have none of the indications for an antibiotic, low-dose water-soluble vitamin A (Aquasol A or genetic) can be used. On the other hand, severe resistant inflammatory acne will often be benefited by 300,000-400,000 units daily. Therapy at these levels cannot be maintained indefinitely because of toxicity at this dose level, side-effects

include headache, nausea, a mind eczematous reaction and the potential for hepatotoxicity. It should be used in these doses for less than 1 month and then only in severe, resistant cases.

2.2.6 Estrogens [10] Woman often improve when started on an estrogen-dominant oral contraceptive (Enovid E, Enovid 5, Ovulen, Demulin). These agents are capable of suppressing adrenal androgen production with a resultant decreased sebum excretion rate of approximately 60-80%. The disease is usually worsened with a progesterone-dominant birth-control pill (Lo/Ovral, Norynil 1 or 2, Norlestrin).

2.2.7 Steroids [10] In patients with severe or resistant inflammatory acne, corticosteroids may be used. Therapy with a short course of oral steroids at a dose of 20-40 mg prednisone for 1-2 weekss followed by rapid tapering has often proved beneficial.

2.2.8 Surgery [10] Extraction of comedones provides substantial psychological benefit to both patient and physician. Open comedones frequently recur and closed comedones require substantial pressure to remove. Moderation is suggested. Incising deep-seated cysts and nodules is of unproven benefit. Aspiration with a needle and syringe or intralesional injection with corticosteroids are less scarring and less painful.

2.2.9 Cryotherapy [10] is performed with either liquid nitrogen or carbon dioxide (crushed carbon dioxide in a mixure of precipitated sulfur and acetone). Liquid nitrogen sprated onto the fluctuant lesions will aid in their resolution. Freezes must be light and superficial so as not to induce further scarring. It has some mild benefit.

2.2.10 Ultraviolet light [10] The summer sun improves many cases of acnes, in some, the increased perspiration may lead to an initial brief exacerbation of disease activity. UV light may also precipitate reactions in those on minocycline (Minocin), doxycycline, and tretinoin (Retin-A) therapy as well as inducing further age-related skin changes. In some patients with severe acne, therapy with sun lamps or UVB

boxes is of benefit. Only inflammatory elements are improved comedonal acne is unchanged or worsened. The routine use of sun-lamp therapy in routine acne is probably unwise.

2.2.11 Miscellaneous treatment [10]

Zinc Therapy with zinc sulfate (220 mg tid) has been claimed to improve imflammatory acne. Double-blind studies suggest it either offers statistically significant improvement over placebo therapy or no significant benefit at all. If used, a moderate dose of only 50 mg, twice daily as placebo herapy, is suggested.

Cimetidine, 300 mg, 5 times daily, suppresses inflammatory acne. Although administration with tetracycline theoretically decreases the absorption of this antibiotics offer improvement in some patients resistant to routine therapy. It functions as an antiandrogen, blocking peripheral conversion of testosterone to dihydrotestosterone.

2.2.12 Scar improvement [10] Significant improvement can be achieved either with the use of collagen implants (Zyderm) or the more traditional dermabrasion. For deep “ice-pick” scars, punch grafting or excision and suturing is necessary.

2.3 Acne associated bacteria

2.3.1 *Staphylococcus aureus* [11]

Staphylococcus aureus is a highly successful opportunistic pathogen. It is a frequent colonizer of the skin and mucosa of humans and animal and can produce a wide variety of diseases.

2.3.1.1 Morphology

Staphylococcus aureus is gram-positive bacteria that occur singly and in pairs, short chains, and irregular grapelike clusters.

2.3.1.2 Biochemical characteristics

Staphylococcus aureus should be inoculated on blood agar and into rich liquid media. With *S. aureus*, abundant growth occurs normally within 18 to 24 hours. Phenotypic tests for species identification include coagulase tests and

agglutination tests, which detect the presence of surface determinants. Antibiotic-resistance tests(Oxacillin 1 µg/mL) using agar diffusion method when clear zone ≤ 10 mm is methicillin resistant *Staphylococcus aureus*.

2.3.2 *Propionibacterium acnes* [7]

P.acnes was first isolated from acne vulgaris. *P.acnes* is anaerobic bacteria. In many types of infection such as upper respiratory tract infections, empyema, skin and soft tissue infections, otitis media, peritoneal abscesses, all of these conditions associated with *P.acnes* . *P.acnes* is pathogenesis of acne vulgaris because of it is typical resident bacteria of human sebaceous follicle and the disease name was derived from the organism.

2.3.2.1 Morphology

P.acnes is a Gram positive bacterium that belong to the normal skin flora. It is nonmotile, nonsporing rods, but in general the classical Propionibacteria tend to be shorter and rather thicker, although all strain may be very variable in morphology, especially in early log phase culture. Strain of *P.acnes* in particular has given long slender irregular rods in young cultures.

2.3.2.2 Biochemical characteristics

P.acnes is anaerobic to aerotolerant. The majority of first isolates grow initially only in aerobic atmosphere but may show facultatively anaerobic growth after several transfers. About one-third of strains are found to be carbon dioxide dependent rather than anaerobic on first isolation. The biochemical characteristics of *P.acnes* were summarized and shown in Table 2.1

Table 2.1 Some biochemical characteristics of *P.acnes*

Optimum growth temperature	37˚C
Catalase	+
Gelatin liquefaction	+
Indole production	+
Nitrate reduction	+
Esculin hydrolyzed	-
Strach hydrolyzed	+
Arabinose	+
Dextrose	+
Fructose	+
Lactose	-
Maltose	-
Mannose	+
Mannitol	-
Salicin	-
Sucrose	-
Xylose	+
Lecithinase	+
Lipase	+

2.4 Plants

2.4.1 *Garcinia mangostana* Linn. [27]

The mangosteen is in genus Garcinia. The scientific name is *Garcinia mangostana* Linn Tree, 10-12 m high; sap yellow. Leave simple, opposite, ovate or elliptic, 6-11 cm wide, 15-25 cm long, thick-coriaceous, shining-glabrous, dark green above, dull pale green beneath. Flower(s) solitary or dichasium, axillary in uppermost leaf-axis, polygamo-monoecious, yellowish green with red edges or almost entirely red, succulent. Fruit berry, depressed-globose, dark purple, 1-3-seeded.

Dried fruit rind: contains tannin, xanthones; treatment of diarrhea and dysentery;antifungal; anti-inflammatory. Xanthones, in vitro test possess antibacterial activity against *Staphylococcus* spp. both normal and penicillin-resisted strain. It was commercialized as cosmetic cream for anti-acne, black scars on the face and boils. The studies about antimicrobial properties of *Garcinia mangostana* Linn are summarized as followed:

Werayut P. et al. [12] studied contents of bioactive components, free radical scavenging and anti-acne producing bacteria activities of young and mature fruit rind extracts of mangosteen were compared and found that the young fruit rind extract contained significantly higher contents of phenolics and tannins and promoted higher free radical scavenging activity than the mature fruit rind extract, while the mature fruit rind extract contained higher contents of flavonoids and α-mangostin xanthone and gave higher anti-acnes producing bacteria activity than the young fruit rind extract. Thus, the young and mature storages of mangosteen fruit rind should be beneficial for development anti-acne pharmaceutical preparations.

Mullika T.C. et al. [13] studied antimicrobial activities of Thai medicinal against these etiology agent of acne vulgaris. The results showed that *Garcinia mangostana* Linn extract had the greatest antimicrobial effect on *Propionibacterium acnes* and *Staphylococcus epidermidis*. In bioautography assay, the *Garcinia mangostana* extract produced strong inhibition zones against *P. acnes*. Antimicrobial activity from fractions of column chromatography had one of the active compounds in *Garcinia mangostana* could be mangostin, xanthone derivative.

Pedraza-Chaverri J. et al. [17] demonstrated that extract of *Garcinia mangostana* Linn (GML) has antioxidant, antitumoral, antitiallergic, anti-inflamma tory, antibacterial and antiviral activities. The pericarp of GML is source of xanthones and other bioactive substances. Xanthones have been isolated from pericarp, whole fruit, heartwood and leaves.

Lih-Geeng C. et al. and Yodhnu S. [14,22] studied anti-inflammatory drug in Southeast Asia. Two xanthones, α- and γ-mangostin, were isolated from the fruit hull of G. *mangostana*, and both significantly inhibited nitric oxide (NO) and PGE_2 production from lipopolysaccharide (LPS)-stimulated RAW 264.7 cells.

Sakagani Y. et al. [23] found that mangostin in mangosteen extract was active against vancomycin resistant *Enterococci* (VRE) and methicillin resistant *Staphylococcus aureus* (MRSA), with MIC values of 6.25 and 6.25 to 12.5 µg/ml, respectively.

2.4.2 *Psidium guajava* Linn. [27]

The scientific name is *Psidium guajava* Linn. Tree is 3-10 m high with stem bark glabrous. Leaves are simple, opposite, elliptic or oblong-elliptic, 3-8 cm long. Flower(s) are solitary or few-flowered cyme, axillary, white, caduceus; stamens numerous. Fruit is globose berry.

Leaf is antidiarrheal, antidysenteric; externally used as deodorant in mouthwash. Root can be used for abnormal urination. Clinical study on antidiarrheal effect showed that 500 mg. dried powder taken every 3 hours for three days is better than tetracycline.

Gnan S.O. et al. [16] compared the antimicrobial activity of Alhodo-mato (*Allium sativon*), Traoeraba (*Commellina beghlensis*) and Goiaba (*Psidium guajava*). The results revealed that Goiaba leaf extract at a concentration of 8 and 40 mg/ml showed promising results. As Goiaba leaf extract showed good antimicrobial activity against *Staphylococcus aureus* at a concentration of 6.5 mg/ml.

2.4.3 Cinnamonum verum J. Presl [28]

The scientific name is Cinnamonum verum J. Presl**.** It has Large tree reaching a height of 10-20 m. All parts are glabrous. Leaves are alternate, short-petioled, rigidly coriaceous, acute or slightly obtuse at the apex, triplinerved base, shining dark-green above, pale beneath. Influorescence in axillary or terminal cymose panicle; flowers white. Drupe is ovoid, glabrous, purplish-brown when ripe.

Tree bark can be collected during summer and autumn. The bark obtained is dried in the shade. An essencial oil can be obtained by distillation.

The bark possesses antibacterial, circulatory, respiratory, uterotonic and stomachic properties. It is applies in the therapy of dyspepsia, colic, diarrhea, dysentery, menstrual haematometra, coryza, influenza, cough, asthma, paresis and snake-bite. It is administered in a daily dose of 1 to 4 g, in the form of a decoction, infusion, powder, pills or juice obtained by grinding it up with water. It is also recommended as a tonic. The essential oil from the bark is a constituent of balsams. The studies about antimicrobial properties of Cinnamonum verum J. Presl are summarized as followed:

Shang-Tzen C. et al.[19] investigated the essential oils from leaves of two *Cinnamonum osmophloeum* clones (A and B) and their chemical constituents. The antibacterial tests demonstrated the indigenous cinnamon B leaf essential oils had an excellent inhibitory effect. The MIC was 500 µg/ml. Cinnamaldehyde possessed the strongest antibacterial activity compare to the other constituents of the essential oils.

Goni P. et al. [20] tested antibacterial activity of the vapour generated by a combination of cinnamon and clove essential oils against the growth of four Gram-negative and four Gram-negative bacteria. It is the first time to demonstrate a combination of essential oils in the vapour phase to prevent microorganism.