Lindera aggregata (Sims) Kosterm: Review on phytochemistry and biological activities

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Abstract: The genus Lindera consists of approximately 100 species that are widely distributed in tropical and subtropical areas throughout the world. Most Lindera plants, particularly Lindera aggregata, is a well-known traditional Chinese medicine that has important medicinal value and health benefits. Contemporary chemical and pharmacological studies have shown that L. aggregata are a source of structurally diverse molecules having pharmacological potential. In an effort to promote research on L. aggregata and develop therapeutic and pharmacological products, this review describes the structural diversity of its components and pharmacological and biological significance of L. aggregata. This review is based on a literature analysis of scientific journals from electronic sources, such as Science Direct, PubMed, Google Scholar, Scopus and Web of Science. Thus, with the growing interest in traditional medicine and botanical drugs worldwide, L. aggregata will increasingly capture chemists’ and pharmacologists’ attention because they produce diverse and structurally novel compounds having pharmacological significance.

Keywords: Lauraceae; Lindera aggregata; Phytochemistry; Sesquiterpenoid; Alkaloid; Phenolic.

Resumen: El género Lindera consta de aproximadamente 100 especies que están ampliamente distribuidas en áreas tropicales y subtropicales en todo el mundo. La mayoría de las plantas de Lindera, particularmente Lindera aggregata, es parte conocida de la medicina tradicional china con un importante valor medicinal y beneficios para la salud. Estudios químicos y farmacológicos contemporáneos han demostrado que L. aggregata es una fuente de moléculas estructuralmente diversas que con potencial farmacológico. En un esfuerzo por promover la investigación sobre L. aggregata y desarrollar productos terapéuticos y farmacológicos, esta revisión describe la diversidad estructural de sus componentes y la importancia farmacológica y biológica de L. aggregata. Esta revisión se basa en un análisis de literatura de revistas científicas de fuentes electrónicas, como Science Direct, PubMed, Google Scholar, Scopus y Web of Science. Por lo tanto, el creciente interés en la medicina tradicional y las drogas botánicas en todo el mundo, L. aggregata captará cada vez más la atención de los químicos y farmacólogos debido a que producen compuestos diversos y estructuralmente novedosos que tienen importancia farmacológica.

Palabras clave: Lauraceae; Lindera aggregata; Fitoquímica; Sesquiterpenoide; Alcaloide; Fenólico.

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INTRODUCTION
For centuries, botanical remedies have been used for human disease management because plants contain multitude of novel components of diverse therapeutic value. The Lauraceae family is by far the largest family of the order Laurales with about 50 genera and over 2000 species distributed throughout tropical to subtropical latitudes especially in Southeast Asia and tropical America (Van der Werff & Richter, 1996; Salleh et al., 2015). Most of the plants of this family and particularly genus *Lindera* are of great interest to pharmacists as preliminary pharmacological studies proved that these plants have the efficient medicinal potential for the treatment of broad-spectrum health disorders (Cao et al., 2016). The genus *Lindera* consists of approximately 100 species that are widely distributed in tropical, subtropical, and temperate zones of Asia and Midwestern America (Tsui, 1987). *Lindera* plants are rich in essential oils and are used for producing spices, fragrances, and building timber. It also reported that the plants are appropriate for manufacturing soaps and lubricants (Flora of China Editorial Committee, 2010).

*Lindera aggregata* (Sims.) Kosterm. (Lauraceae) (Figure No. 1) is an important medicinal plant, widely distributed in China, Japan, Taiwan, and Southeast Asia (Li, 1984). In China, it is locally known as *Wu Yao*, while in Japan known as *Uyaku*. *L. aggregata* is an evergreen shrub or small tree that is widely distributed and common across the eastern moist subtropical evergreen broadleaved forests (Wang et al., 2007). Some isolated outposts have also been reported from Vietnam and the Philippines and the species is sometimes cultivated outside its native range. The plant grows on sunny mountain slopes, in sparse forests and thickets at elevations between 200 and 1,000 m. It is dioecious, produces entomophilous flowers and fleshy drupes that are putatively dispersed by birds (Hirayama et al., 2004). The Flora of China and The Plant List recognize two varieties which are *L. aggregata* var. *hemsleyana* (Diels) S.S.Ying and *L. aggregata* var. *playfairii* (Hemsl.) H.B. Cui (The Flora of China, 2010; The Plant List, 2010). Previous phytochemical investigations revealed that sesquiterpenoids are the main secondary metabolites isolated from this plant.

Due to its diverse applications, wide attention has been paid by scientific communities and plenty of investigations on bioactive constituents and pharmacological activities have been conducted. At this time, we summarize research findings on phytochemistry and their pharmacological activities. This highlights the current status and likely future directions that will provide a representative overview of this medicinal plant. The scientific databases: Google Scholar, Web of Science, PubMed, and Scopus were utilized to gather all relevant information from literature articles.

![Figure No. 1](Lindera aggregata (Sims.) Kosterm.)

**Traditional uses**
There is a long history of using *L. aggregata* in traditional Chinese medicine for the treatment of various diseases. *L. aggregata* extracts is usually used for treating urinary system diseases such as enuresis and urinary stones. Besides, it has pronounced effects on chronic gastritis and rheumatoid arthritis (Zhang & Wang, 2000). In addition, mashed leaves of *L. aggregata* are beneficial for treating mastitis, acute cellulitis, and carbuncles (Chou et al., 2000). Fresh cut leaves of *L. aggregata* stir-fried in rice wine show the therapeutic effect on rheumatoid arthritis. In addition, *L. aggregata* extracts are used in Japan to treat stroke and cholera (Han et al., 2008).

**PHYTOCHEMISTRY**
A review of the literature revealed that few phytochemical studies have been carried out on *L. aggregata*. The studies have reported the presence of several classes of secondary metabolites including sesquiterpenoids, amides, alkaloids, flavonoids, procyanidins, lignans, benzenoids, butenolides, phenolics, and essential oils. The isolated phytochemicals are tabulated in Table No. 1.

| Phytochemical Class       | Examples                                      |
|---------------------------|-----------------------------------------------|
| Sesquiterpenoids          | *L. aggregata*                                |
| Amides                    | *L. aggregata*                                |
| Alkaloids                 | *L. aggregata*                                |
| Flavonoids                | *L. aggregata*                                |
| Procyanidins              | *L. aggregata*                                |
| Lignans                   | *L. aggregata*                                |
| Benzenoids                | *L. aggregata*                                |
| Butenolides               | *L. aggregata*                                |
| Phenolics                 | *L. aggregata*                                |
| Essential oils            | *L. aggregata*                                |
Table No. 1
Phytochemicals isolated from *Lindera aggregata*

| No | Constituents                  | Parts          | References     |
|----|------------------------------|----------------|----------------|
| 1  | Aggreganoid A                | Roots          | Liu *et al.*, 2009a |
| 2  | Aggreganoid B                | Roots          | Liu *et al.*, 2009a |
| 3  | Aggreganoid C                | Roots          | Liu *et al.*, 2009a |
| 4  | Aggreganoid D                | Roots          | Liu *et al.*, 2009a |
| 5  | Aggreganoid E                | Roots          | Liu *et al.*, 2009a |
| 6  | Aggreganoid F                | Roots          | Liu *et al.*, 2009a |
| 7  | Linderalide A                | Roots          | Liu *et al.*, 2009b |
| 8  | Linderalide B                | Roots          | Liu *et al.*, 2009b |
| 9  | Linderalide C                | Roots          | Liu *et al.*, 2009b |
| 10 | Linderalide D                | Roots          | Liu *et al.*, 2009b |
| 11 | Linderalide A                | Root tubers    | Qiang *et al.*, 2011 |
| 12 | Linderalide B                | Root tubers    | Qiang *et al.*, 2011 |
| 13 | Linderalide C                | Root tubers    | Qiang *et al.*, 2011 |
| 14 | Linderalide D                | Root tubers    | Qiang *et al.*, 2011 |
| 15 | Linderalide E                | Root tubers    | Qiang *et al.*, 2011 |
| 16 | Linderalide F                | Root tubers    | Qiang *et al.*, 2011 |
| 17 | Linderanine A                | Root tubers    | Qiang *et al.*, 2011 |
| 18 | Linderanine B                | Root tubers    | Qiang *et al.*, 2011 |
| 19 | Linderanine C                | Root tubers    | Qiang *et al.*, 2011 |
| 20 | (+)-Linderadine              | Root tubers    | Qiang *et al.*, 2011 |
| 21 | ent-4(15)-Eudesmene-1β,6α-diol | Root tubers | Qiang *et al.*, 2011 |
| 22 | Dehydrocostuslactone         | Root tubers    | Qiang *et al.*, 2011 |
| 23 | Linderagalactone A           | Root tubers    | Gan *et al.*, 2009a |
| 24 | Linderagalactone B           | Root tubers    | Gan *et al.*, 2009a |
| 25 | Linderagalactone C           | Root tubers    | Gan *et al.*, 2009a |
| 26 | Linderagalactone D           | Root tubers    | Wu *et al.*, 2010 |
| 27 | Linderagalactone E           | Root tubers    | Wu *et al.*, 2010 |
| 28 | 3-Eudesmene-1β,11-diol        | Root tubers    | Gan *et al.*, 2009a |
| 29 | Hydroxylindestenolide        | Root tubers    | Gan *et al.*, 2009a |
|    |                              | Leaves         | Zhang *et al.*, 2001 |
|    |                              | Root tubers    | Qiang *et al.*, 2011 |
|    |                              | Roots          | Wu *et al.*, 2010 |
|    |                              | Roots          | Ma *et al.*, 2015 |
| 30 | Dehydrolindestrenolide       | Leaves         | Zhang *et al.*, 2001 |
| 31 | Strychnistenolide            | Root tubers    | Gan *et al.*, 2009a |
| 32 | Hydroxyisogermafurenolide    | Root tubers    | Gan *et al.*, 2009a |
| 33 | Atractylenolide III          | Root tubers    | Gan *et al.*, 2009a |
| 34 | Linderane                    | Root tubers    | Gan *et al.*, 2009a |
|    |                              | Roots          | Cheng *et al.*, 2007 |
|    |                              | Roots          | Wu *et al.*, 2010 |
|    |                              | Root tubers    | Qiang *et al.*, 2011 |
| 35 | Neolinderalactone            | Root tubers    | Gan *et al.*, 2009a |
|    |                              | Roots          | Wu *et al.*, 2010 |
| 36 | Neolindenemononelactone      | Roots          | Cheng *et al.*, 2007 |
| 37 | Isolinderalactone            | Roots          | Cheng *et al.*, 2007 |
| 38 | Linderalactone               | Root tubers    | Gan *et al.*, 2009a |
|   | Name                                      | Source                                                                 |
|---|------------------------------------------|------------------------------------------------------------------------|
| 39| 8-Hydroxylindestenolide                  | Wang et al., 2009a                                                    |
| 40| bi-Linderone                             | Wang et al., 2010a                                                    |
| 41| epi-bi-linderone                         | Chen et al., 2018                                                     |
| 42| (±)-Linderaspirone A                    | Chen et al., 2018                                                     |
| 43| (±)-Lindepentone A                      | Chen et al., 2018                                                     |
| 44| Lindoxepines A                           | Chen et al., 2018                                                     |
| 45| Lindoxepines B                           | Chen et al., 2018                                                     |
| 46| (+)-Demethoxy-epi-bi-linderone          | Chen et al., 2018                                                     |
| 47| (-)-Demethoxy-epi-bi-linderone          | Chen et al., 2018                                                     |
| 48| Methylbinderone                          | Chen et al., 2018                                                     |
| 49| Methylucidone                            | Chen et al., 2018                                                     |
| 50| (+)-Norboldine acetate                  | Gan et al., 2009b                                                    |
| 51| (+)-Norboldine                           | Han et al., 2008                                                      |
| 52| (+)-Boldine                              | Han et al., 2008                                                      |
| 53| (+)-Laurotetanine                        | Yang et al., 2020                                                    |
| 54| (+)-N-methyllaurotetanine               | Ma et al., 2015                                                       |
| 55| (+)-Reticuline                           | Ma et al., 2015                                                       |
| 56| (-)-Pronuciferine                        | Yang et al., 2020                                                    |
| 57| Pallidine                                | Ma et al., 2015                                                       |
| 58| Linderaline                              | Ma et al., 2005                                                       |
| 59| Protosinomenine                          | Ma et al., 2005                                                       |
| 60| Laudanosoline 3',4'-dimethyl ether       | Ma et al., 2005                                                       |
| 61| Norisoboldine                            | Ma et al., 2015                                                       |
| 62| Linderagatine                            | Ma et al., 2015                                                       |
| 63| Linderagrine A                           | Kuo et al., 2014                                                      |
| 64| N-trans-feruloyltyramine                 | Ma et al., 2015                                                       |
| 65| N-cis-feruloyltyramine                   | Ma et al., 2015                                                       |
| 66| N-trans-feruloylmethoxytyramine          | Ma et al., 2015                                                       |
| 67| (+)-Isoboldine                           | Ma et al., 2015                                                       |

**AMIDES AND ALKALOIDS**

|   | Name                                      | Source                                                                 |
|---|------------------------------------------|------------------------------------------------------------------------|
| 60| Launderosamine 3',4'-dimethyl ether       | Ma et al., 2015                                                       |
| 61| Norisoboldine                            | Ma et al., 2015                                                       |
| 62| Linderagatine                            | Ma et al., 2015                                                       |
| 63| Linderagrine A                           | Kuo et al., 2014                                                      |
| 64| N-trans-feruloyltyramine                 | Ma et al., 2015                                                       |
| 65| N-cis-feruloyltyramine                   | Ma et al., 2015                                                       |
| 66| N-trans-feruloylmethoxytyramine          | Ma et al., 2015                                                       |
| 67| (+)-Isoboldine                           | Ma et al., 2015                                                       |
|   | Compound                                | Source     | Reference          |
|---|-----------------------------------------|------------|--------------------|
| 68| Thalifoline                             | Roots      | Yang et al., 2020  |
| 69| Northalifoline                          | Roots      | Ma et al., 2015    |
| 70| Yuzirine                                | Roots      | Ma et al., 2015    |
| 71| (1'S)-12'-Hydroxyl-linderegatine         | Roots      | Yang et al., 2020  |
| 72| (1S)-5'-O-p-Hydroxybenzoyl norretilicine| Roots      | Yang et al., 2020  |
| 73| (1R, 1'R)-11,11'-Biscreolauritanine      | Roots      | Yang et al., 2020  |
| 74| Costarcine                              | Roots      | Yang et al., 2020  |
| 75| Actinodaphnine                          | Roots      | Yang et al., 2020  |
| 76| Laurolitsine                            | Roots      | Yang et al., 2020  |
| 77| Norjuziphine                            | Roots      | Yang et al., 2020  |
| 78| Reticuline n-oxide                      | Roots      | Yang et al., 2020  |
| 79| Boldine n-oxide                         | Roots      | Yang et al., 2020  |
| 80| N-methylaurotetanine n-oxide            | Roots      | Yang et al., 2020  |
| 81| Salutaridine n-oxide                    | Roots      | Yang et al., 2020  |
| 82| Lindoldhamine                           | Roots      | Yang et al., 2020  |
| 83| Secolaurolitsine                        | Roots      | Yang et al., 2020  |
| 84| Secoboldine                             | Roots      | Yang et al., 2020  |

### FLAVONOIDS

|   | Compound                                | Source     | Reference          |
|---|-----------------------------------------|------------|--------------------|
| 85| Quercetin                               | Leaves     | Xiao et al., 2011  |
| 86| Quercetin-3-O-α-D-arabinofuranoside      | Leaves     | Xiao et al., 2011  |
| 87| Quercetin-3-O-α-D-glucopyranoside        | Leaves     | Xiao et al., 2011  |
| 88| Quercetin-3-O-α-L-rhamnopyranoside      | Leaves     | Han et al., 2008   |
| 89| Quercitrin                              | Leaves     | Xiao et al., 2011  |
| 90| Kaempferol                              | Leaves     | Xiao et al., 2011  |
| 91| Kaempferol-3-O-L-rhamnoside             | Leaves     | Xiao et al., 2011  |
| 92| Kaempferol-3-O-D-glucopyranoside        | Leaves     | Xiao et al., 2011  |
| 93| Dihydrokaempferol-3-O-L-rhamnoside      | Leaves     | Xiao et al., 2011  |

### PROCYANIDINS

|   | Compound                                | Source     | Reference          |
|---|-----------------------------------------|------------|--------------------|
| 94| Procyanidin B1                          | Leaves     | Zhang et al., 2003 |
| 95| Cinnamtannin B1                         | Leaves     | Zhang et al., 2003 |
| 96| Cinnamtannin B2                         | Leaves     | Zhang et al., 2003 |

### LIGNANS

|   | Compound                                | Source     | Reference          |
|---|-----------------------------------------|------------|--------------------|
| 97| rel- (2α,3β)-7-O-methylcedrusin         | Roots      | Ma et al., 2015    |
| 98| (-)-Lyoniresinol                        | Roots      | Ma et al., 2015    |
| 99| Evofolin B                              | Roots      | Ma et al., 2015    |

### BENZENOIDS

|   | Compound                                | Source     | Reference          |
|---|-----------------------------------------|------------|--------------------|
| 100| Linderaagatin A                         | Roots      | Ma et al., 2015    |
| 101| Linderaagatin B                         | Roots      | Ma et al., 2015    |

### BUTENOLIDES

|   | Compound                                | Source     | Reference          |
|---|-----------------------------------------|------------|--------------------|
| 102| Secoaggregatalactone A                  | Leaves     | Lin et al., 2007   |

### PHENOLICS

|   | Compound                                | Source     | Reference          |
|---|-----------------------------------------|------------|--------------------|
| 103| 3-Hydroxy-1-(4-hydroxyphenyl)propan-1-one| Roots      | Ma et al., 2015    |
| 104| p-Hydroxybenzoic acid                   | Roots      | Ma et al., 2015    |
| 105| 4-Hydroxy-3-methoxy acetophenone        | Roots      | Ma et al., 2015    |
| 106| Methyl 3,5-dimethoxy-4-hydroxybenzoate  | Roots      | Ma et al., 2015    |
| 107| Vanillic acid                           | Roots      | Ma et al., 2015    |
| 108| Tyrosol                                 | Roots      | Ma et al., 2015    |
| 109| 2-(4-Hydroxy-3-methoxyphenyl)-ethanol   | Roots      | Ma et al., 2015    |
| 110| 2-(4-Hydroxy-3,5-dimethoxyphenol)-ethanol| Roots     | Ma et al., 2015    |
| 111| 2,6-Dimethoxy-p-benzoquinone            | Roots      | Ma et al., 2015    |
**Sesquiterpenoids**

A total of forty-nine sesquiterpenoids (1-49), including dimeric and trimeric sesquiterpenoids have been reported phytochemically from *L. aggregata*. The chemical structures are shown in Figure No. 2. Liu et al. (2009a) were successfully isolated and characterized six unprecedented sesquiterpenoid trimmers and dimers, aggregenoids A-F (1-6) from the ethanolic extract of the roots of *L. aggregata*. These compounds represent a new class of oligomeric sesquiterpenoids featuring the connection between different or identical sesquiterpenoid monomers via a carbon bridge. The new linkage pattern of these compounds is not only crucial for the chemical diversity and biosynthesis of oligomeric sesquiterpenoids, but also the chemotaxonomic studies on genus *Lindera*. In the same year, the authors also managed to isolate four desesquiterpenoid-geranylbenzofuranone conjugates, linderalides A-D (7-10) from the same part. These compounds represent the first examples of desesquiterpenoid-geranylbenzofuranone hybrids directly linked by two C–C bonds. Another compound was linderalide D (10), which bears an unprecedented carbon skeleton featuring an unusual linearly 6/6/5/6/6 pentacyclic ring system fused by a sesquiterpenoid unit and a geranylbenzofuranone moiety.

In another study, Chen et al. (2018) were reported a novel skeleton of 3,5-dioxocyclopent-1-enecarboxylate, known as (±)-lindependentone A (43), together with an unprecedented oxepine-2,5-dione derivative skeleton, lindoxepines A-B (44-45). The authors also suggest that compound (44-45) might be the key intermediates for the synthesis of *Lindera* cyclopentenediones. Besides, Qiang et al. (2011) have successfully isolated six new sesquiterpenoids, known as linderanlde A-F (11-16) from the root tubers part. Linderanlde A (11) is a C-8 epimer of linderanine C (19). Meanwhile, Wang et al. (2010a) reported the isolation of a racemate, bi-linderone (40) from the roots part. The compound represents the first member of an unprecedented class of spirocyclopentene diones. Although it shares its structural features with the cyclopentenedione derivative methyl-linderone (48), it has a backbone with 34 carbon atoms that includes a unique spiro ring, which is unprecedented in the field of natural products. In the meantime, the authors also managed to isolate a pair of natural windmill-shaped enantiomers, known as (±)-linderaspirone A (42). The biogenetic route to linderaspirone A (42) was proposed to be a formation by a [4+4] cycloaddition from the monomer methyl linderone (48). Furthermore, Gan et al. (2009a) were reported the identification of five new sesquiterpene lactones, named as linderagalactones A-E (23-27) from the roots part. In addition, Cheng et al. (2007) were managed to characterize a new sesquiterpene, neolindenenonelactone (35), along with linderene (34), isolinderalactone (37), linderalactone (38), and 8-hydroxylindostenolide (39).

**Amides and alkaloids**

Thirty-five alkaloids including amides (50-84) were successfully identified from the roots of *L. aggregata*. The chemical structures are shown in Figure No. 3. Gan et al. (2009b) was reported the isolation of new alkaloid, (+)-norboldine acetate (50) together with (+)-norboldine (51), (+)-boldine (52), (+)-laurotetanine (53), (+)-N-methyllaurotetanine (54), (+)-reticuline (55), (-)-pronuciferine (56), and pallidine (57) from the roots of *L. aggregata*. A year before, the authors also reported a novel bisbenzylisoquinoline alkaloid, linderegatine (62), as well as two known isoquinoline alkaloids reticuline (55) and pallidine (57) from the same part (Gan et al., 2008).

Another study, Chou et al. (2005) was successfully identified a new aporphinoid alkaloid, named as linderaline (58), along with eight known isoquinoline alkaloids, identified as pallidine (57), protosinomenine (59), laudanosoline 3′,4′-dimethyl ether (60), boldine (52), norisoboldine (61), norboldine (51), pronuciferine (56), and reticuline (55) from the ethanol extract of the dried roots part. In addition, Kuo et al. (2014) managed to isolate a new β-carboline alkaloid, linderaggrine A (63) from the roots part of *L. aggregata*. β-Carboline alkaloids are a prevalent class of biologically active natural products and this is the first report from this plant. Recently, Yang et al. (2020) were successfully...
characterized three new benzyloquinoline alkaloids, (1'R)-12'-hydroxyl-linderegateine (71), (1S)-5'-O-p-hydroxybenzoyl norreticuline (72), and (1R,1'R)-11,11'-biscoclaurine (73), along with eighteen known compounds.

Flavonoids
Nine flavonoids (85-93) have been isolated from the leaves of L. aggregata. The chemical structures are shown in Figure No. 4. Xiao et al. (2011) successfully characterized eight known flavonoids, identified as quercetin (85), quercetin-3-O-α-D-arabinofuranoside (86), quercetin-3-O-α-D-glucopyranoside (87), quercetin-3-O-L-rhamnopyranoside (88), kaempferol (90), kaempferol-3-O-L-rhamnopyranoside (91), kaempferol-3-O-D-glucopyranoside (92), and dihydrokaempferol-3-O-L-rhamnopyranoside (93). Compounds (91-93) were isolated for the first time from this species. Meanwhile, quercitrin (89) and their pharmacokinetics studies have been described by Xu et al. (2017).

Miscellaneous compounds
In addition to the above-mentioned phytochemicals, some other constituents such as procyanidins (94-96), lignans (97-99), benzenoids (100-101), butenolide (102), and phenolics (103-112) were also identified from the leaves and roots of L. aggregata. The chemical structures are shown in Figure No. 5. Ma et al. (2015) managed to isolate two new benzenoids, identified as linderagatin A and B (100-101), together with three known lignans, rel-(2α,3β)-7-O-methylcedrusin (97), (−)-lyoniresinol (98), and evofolin B (99) from the roots part.

Additionally, the authors also managed to characterize ten known phenolic compounds, which were identified as 3-hydroxy-1-(4-hydroxyphenyl)-propan-1-one (103), p-hydroxybenzoic acid (104), 4-hydroxy-3-methoxy acetonaphone (105), methyl 3,5-dimethoxy-4-hydroxybenzoate (106), vanillic acid (107), tyrosol (108), 2-(4-hydroxy-3-methoxyphenyl)-ethanol (109), 2-(4-hydroxy-3,5-dimethoxyphenyl)-ethanol (110), 2,6-dimethoxy-p-benzoquinone (111), and 6′-O-vanilloxytachioside (112). Meanwhile, Lin et al. (2007) were successfully isolated a new secobutanolid, secocaggregatalactone A (102) from the leaves part. Moreover, three procyanidins were reported by Zhang et al. (2003), characterized as procyanidin B1 (94), cinnamtannin B1 (95), and cinnamtannin B2 (96).

Essential oils
Three studies have been reported on the essential oil of L. aggregata. Analysis of the root tubers oil of L. aggregata led to the identification of α-longifolene (15.13%), bornyl acetate (11.49%), and α-eudesmol (9.14%) as the major components (Du et al., 2003). In another study, the leaves oil-rich of sesquithuriferol (35.90%), 14-oxo-α-muurolene (16.45%) and 1,8-cineole (5.34%) (Fu et al., 2009). Nevertheless, lindene (19.21%), linderene (16.83%), bornyl acetate (8.26%) and linderene acetate (8.17%) were main constituents of the essential oil of L. aggregata roots from Jiangxi Province while that from Fujian Province contained β-phellandrene (16.23%) followed by lindene (14.90%), linderene (12.83%), and linderene acetate (9.29%) (Wu et al., 2010). The above findings suggested that the essential oil content of L. aggregata and its composition showed considerable variations and maybe due to plant origin, ecological and climatic conditions as well as storage duration of medicinal herbs.

Biological activities
The literature study reveals the need for a thorough investigation of the pharmacological characteristics of the extracts and isolated compounds from L. aggregata. The biological activities including antihyperlipidemic, anti-inflammatory, cytotoxicity, insecticidal, antifulmic, hepatoprotective, gastrointestinal, and mutagenicity have been reported in some works.

Urox is an herbal formulation containing concentrated extracts of L. aggregata root, Crataeva nurvala stem bark, and Equisetum arvense stem, have well established traditional uses and reported safe for human consumption (Deshpande et al., 1982). Besides, Schoendorfer et al. (2018) demonstrated viability of this herbal combination to serve as an effective treatment, with minimal side-effects, based on results of the treatment of symptoms of overactive bladder and urinary incontinence.

In addition, the extracts have been used traditionally to treat some types of ailments have not been investigated for their biological activities at all. Thus, this is an opportunity to find new pharmacological properties from this species, not to mention promising sources for drugs. Furthermore, their toxicity has not been studied. The information on the qualification of the extracts is very important to be applied as drugs.
Figure No. 2
Chemical structures of sesquiterpenoids
Figure No. 2 (continue)
Chemical structures of sesquiterpenoids
Chemical structures of amides and alkaloids

Figure No. 3

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**Antihyperlipidemic**

The aqueous leaves extract of *L. aggregata* showed significantly reduced serum triglyceride (TG), alanine aminotransferase level (ALT), but elevated faecal TG in normal mice. It also remarkably lowered serum total cholesterol (TC), TG, low-density lipoprotein (LDL), N-HDL, ALT, hepatic lipid/glucose (GLU), apolipoprotein B (APOB), hepatic GLU and increased serum high-density lipoprotein (HDL), apolipoprotein A1 (APOA-I), faecal TG levels in hypercholesterolemic (HCL) mice. These results revealed that the extract treatment regulated the disorders of the serum lipid and liver function, reduced hepatic GLU contents both in normal and HCL mice (Zhu et al., 1998; Wang et al., 2020).

**Anti-inflammatory**

Aggreganoid A (1) was reported to inhibit the TGF-β induced Smad2 protein phosphorylation in a dose-dependent manner in A549 cells, and suggested to have potential as TGF-β inhibitor. However, no significant activity of aggreganoids A-F (1-6) was reported against A549 and SH-SY5Y cell lines (Liu et al., 2009a). Meanwhile, linderaspirone A (42) was found markedly elevated phosphorylation of InsR, Akt, and GSK-3β under insulin-resistant condition (Wang et al., 2010b). Furthermore, norisoboldine (61) and boldine (52) showed inhibitory activities on nitric oxide production induced by lipopolysaccharide in mouse macrophage RAW 264.7 cells, with IC50 values of 37.8 and 38.7 μM, respectively (Yang et al., 2020).

**Cytotoxicity**

(+)-Norboldine (51) showed weak activity against the mouse lymphocytic leukemia L1210 cell line with LC50 value 1.1×10^{-4} mol/L (Gan et al., 2009b). Secoaggregatalactone A (102) was found to exhibit noticeable cytotoxicity (EC50 of 6.61 μg/mL) against the human hepatoma cell line (HepG2 cell line). The authors suggested that the compound induced significant apoptotic cell death through the activation of caspase-8, Bid, and caspase-3, leading to cleavage of PARP and causing DNA fragmentation (Lin et al., 2007). In another study, costaricine (74) and laurilitsine (76) showed cytotoxic activities against human colon carcinoma cell line (HCT-116) with IC50 values of 51.4 and 27.1 μM against human cancer cell line (HCT-116), respectively (Yang et al., 2020).

**Insecticidal**

The essential oil of *L. aggregata* was found to possess insecticidal activity against two-grain storage insects, *Sitophilus zeamais* and *Tribolium castaneum* with LC50 values of 61.65 and 18.47 μg/adult, respectively. In addition, the oil showed pronounced fumigant toxicity against *Sitophilus zeamais* and *Tribolium castaneum* which gave LC50 values of 23.04 and 14.69 mg/L air, respectively (Liu et al., 2016).

**Antiulcer**

Zhu et al. (1998) were reported the antiulcer action of the extract of the root of *L. aggregata* against the ethanol-induced ulceration model in rats. The extract was found to produce strong local gastric protective effects and mild systemic effects against ethanol-induced ulcer formation. The protective effect may be mediated by endogenous prostaglandins and regulation of the vagus nerve.
Figure No. 5
Chemical structures of miscellaneous compounds
Hepatoprotective
Lindera galactone E (27), linderane (34), hydroxylindenestenolide (29), and linderalactone (38) have shown hepatoprotective activity against H2O2-induced oxidative damages on HepG2 cells with EC50 values of 67.5, 167.0, 42.4, and 98.0 μM, respectively (Gan et al., 2009a).

Gastrointestinal
It has been documented that L. aggregata extract can regulate gastric motility and the essential oil fraction was able to increase the contraction of the intestines, so it can be used as a carminative to treat abdominal distension (Li, 1992).

Mutagenicity
The ethanolic L. aggregata roots extract showed a significant inhibitory mutagenicity effect on the 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]-indole (Trp-P-1) by the Ames assay (Niikawa et al., 1995).

CONCLUSION
Until now, significant progress has been witnessed in phytochemistry and pharmacology of L. aggregata. Thus, some traditional uses have been well supported and clarified by modern pharmacological studies. Moreover, L. aggregata also showed therapeutic potential in the treatment of cardiac, renal, cystic and rheumatic diseases. But present findings are still insufficient that cannot satisfactorily explain some mechanisms of action. More well-designed studies in vitro, especially in vivo, are required to establish links between the traditional uses and bioactivities, discover new skeletons and activity molecules, as well as ensure safety before clinical use. We hope that the information discussed here could make people more aware of L. aggregata and can be beneficial for further research.

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