



## ANTIPROLIFERATIVE EFFECTS OF EMBLICA OFFICINALIS AND METFORMIN ON ORAL CANCER CELL LINE: AN IN VITRO STUDY

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### Abstract

**Introduction:** Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by hyperglycemia, caused mainly by insulin resistance or inadequate insulin production. <sup>1</sup>Emblica officinalis (Amla), is one of the most common medicinal herb used in ayurvedic proprietary medicines.

**Methodology:** EOE is a formulated juice powder extracted from the fruits of E. officinalis fruits (amla). The fruits were crushed in a multi mill and squeezed to remove the separated juice using an industrial centrifuge and further concentrated at low temperature using an evaporator. The resultant thick syrup was formulated with suitable quantity of maltodextrin to obtain a powder with BGG 10–12% in the final product (termed as EOE).

**Results:** A total number of 170 subjects were screened, out of which 126 (75 males and 51 females) were found eligible and were randomized to metformin 500 mg (N = 42), EOE-1 g (N = 42), and EOE-2 g (N = 42). One subject each from metformin 500 mg and EOE-1 g groups were lost to follow-up, and 124 subjects [metformin 500 mg (N = 41), EOE-1 g (N = 41), and EOE-2 g (N = 42)] completed the study.

**Conclusion:** The present data provide strong evidence that EOE (standardized for 10% BGG) at 1 g and 2 g day<sup>-1</sup> is safe, well tolerated and exerted effective antidiabetic and lipid-lowering activities in cancer patients. More importantly, EOE at a dose of 2 g day<sup>-1</sup> showed superior antidiabetic and anticancer activities compared to the pharmaceutical drug, metformin.

**Keyword:** Metformin, Emblica Officinalis, Cancer, Medicinal Plants.

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## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by hyperglycemia, caused mainly by insulin resistance or inadequate insulin production.<sup>1</sup> Insulin deficiency along with metabolic disturbances causes chronic hyperglycemia in T2DM. As per the International Diabetes Federation Atlas guideline report, 463 million people in the age group of 20–79 years were diagnosed with diabetes in 2019, which is predicted to increase to 700 million by 2045.<sup>2</sup> Plenty of medicinal plants are present as a combination in herbal preparation of the Indian traditional healthcare system (Ayurveda), Siddha and Unani system are also recommended for their antioxidant properties. *Emblica officinalis* (Amla), is one of the most common medicinal herb used in ayurvedic proprietary medicines. In India, fruits of *E. officinalis* are widely used as an anti-inflammatory and antipyretic medicine besides its common use as a tonic during winter season. The current review presents the medicinal properties of *E. officinalis* with respect to its molecular mechanisms and allied phytoconstituents. However, the potential of *Emblica Officinalis* extract to be utilized as an anticancer agent has been scrutinized using modern medical techniques over the past two decades. To date, there is substantial evidence that these extracts contain small molecules with both cancer-preventative and antitumor activity. First, *Emblica Officinalis* has potent free radical scavenging activities that might prevent reactive oxygen species induced DNA damage and oncogenesis. However, in the animal models described above, it is unclear to what extent reactive oxygen species contribute to the underlying pathology, implying that there may be alternative mechanisms of action. Second, the extract has properties allowing it to reduce the levels of cytochrome enzymes in liver cells. Cytochromes, such as Cyp 450, convert xenobiotics to potentially carcinogenic substances in an effort to clear them from the body. However, this concept is controversial as Amla extract was not found to decrease Cyp 450 levels in at least two other studies. Third, *Emblica Officinalis* extracts have anti-inflammatory activities that might prevent inflammation related cancers. Finally, as we will describe below, *Emblica Officinalis* harbors potent antitumor activity. Even exposure to low levels of extract from these berries may be enough to impair tumor progression at early stages. It should be noted that there is concern regarding potential hepatotoxicity after long term Amla ingestion. This matter may need to be resolved in the future by

clinical and epidemiological studies before *Emblica Officinalis* extract can be safely recommended for long term consumption for the prevention of cancer.<sup>3</sup> In the present study, we evaluated the effect of *Emblica Officinalis* in reducing oral cancer in comparison with metformin, the first-line treatment for newly diagnosed T2DM patients as per the American Diabetes Association's guidelines. In addition to antihyperglycemic activity, metformin possesses cardioprotective, antihyperlipidemic, and probable anti-cancer activity. Gastrointestinal intolerance and lactic acidosis are the most frequently observed contraindications associated with metformin, which is observed in one-fourth of patients prescribed the drug.

## 2. Methodology

### **Emblica officinalis extract (EOE)**

EOE is a formulated juice powder extracted from the fruits of *E. officinalis* fruits (amla). The fruits were crushed in a multi mill and squeezed to remove the separated juice using an industrial centrifuge and further concentrated at low temperature using an evaporator. The resultant thick syrup was formulated with suitable quantity of maltodextrin to obtain a powder with BGG 10–12% in the final product (termed as EOE). EOE is totally soluble in water. It was free of pesticides, aflatoxins, heavy metals and microbes when tested as per standard or US pharmacopeial methods. BGG in EOE was quantified by HPLC using a C<sub>18</sub> BDS (Thermo), 4.6 × 250 mm with 5 μ particle size, under gradient of two mobile phases namely 0.1% formic acid in water and 100% methanol. Under these conditions, BGG eluted with a retention time of 9.8 min which was detected ( $\lambda_{\text{max}} = 272 \text{ nm}$ ) and quantified to be 10–12% w/w. A typical HPLC chromatogram of EOE is provided in ESI Fig. 1.

### **Clinical study design**

This randomized open-label, three-arm, comparative, multicenter study was conducted in newly diagnosed diabetes patients from A Department of Oral Medicine and Radiology, Faculty of Dental Sciences, RUAS. Patient recruitment started in January 2022 and was completed by February 2023. A total of 126 newly diagnosed diabetes patients with cancer aged 30–65 years who meet all the inclusion criteria were enrolled in this study. The subjects were randomly divided to receive EOE-1 g day<sup>-1</sup> EOE-2 g day<sup>-1</sup> or metformin 500 mg day<sup>-1</sup> for 90 days. Two subjects were lost to follow up and 124 patients completed the study (Fig. 2).

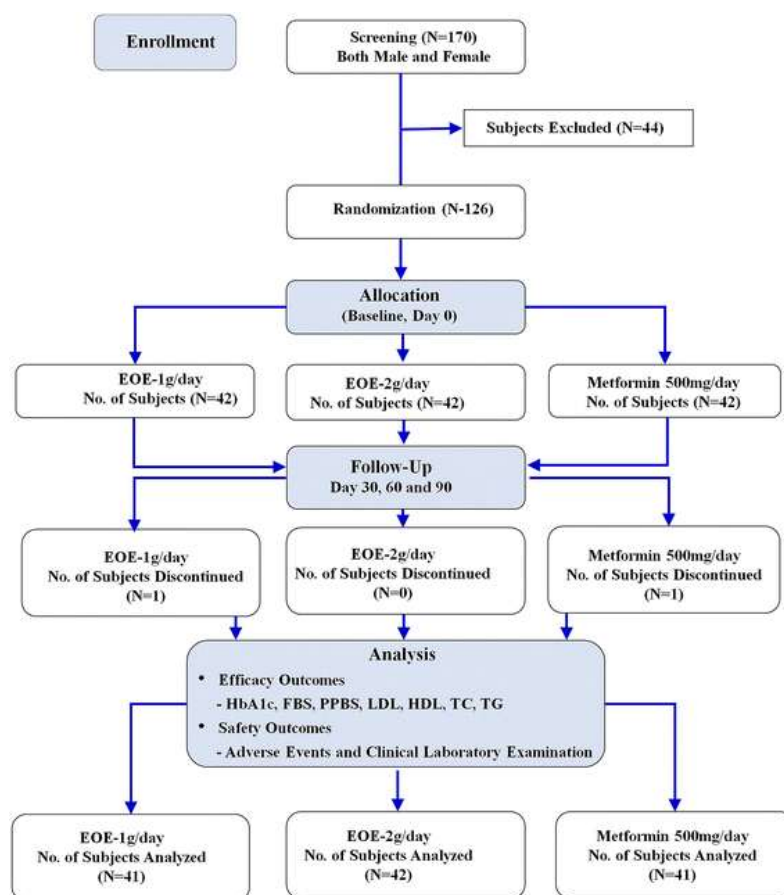


Fig. 2 CONSORT Flow Diagram of *E. Officinalis* Extract (EOE).

### Patient details and ethics

EOE is a formulated juice powder extracted from the fruits of *E. officinalis* fruits (amla). The fruits were crushed in a multi mill and squeezed to remove the separated juice using an industrial centrifuge and further concentrated at low temperature using an evaporator. The resultant thick syrup was formulated with suitable quantity of maltodextrin to obtain a powder with BGG 10–12% in the final product (termed as EOE). Newly diagnosed type 2 diabetes patients in the age group of 30 to 65 years with Body Mass Index (BMI) ranging from 27 to 35 kg m<sup>-2</sup>, FBS 130 to 150 mg dL<sup>-1</sup>, PPBS 210 to 300 mg dL<sup>-1</sup>, hemoglobin A1c (HbA1c) 6.5 to 9.0%, Total Cholesterol (TC) 200–300 mg dL<sup>-1</sup>, low density lipoprotein (LDL) 140 to 299 mg dL<sup>-1</sup>, and TG 160 to 300 mg dL<sup>-1</sup> were included in the study. In addition, all the study participants agreed to do physical activity for a minimum of 30 minutes, five days a week. None of the subjects were taking any concomitant medication at the time of enrollment. Female subjects of reproductive potential who agreed to use a barrier method of contraception throughout the study period were included in the study. Exclusion criteria included subjects having a history of smoking and alcohol intake, type 1 diabetes, chronic gastrointestinal diseases, severe immune deficiency, lactose intolerance, clinically

significant thyroid disorder, cardiovascular, hematological, hepatic, renal, respiratory, active malignancy, or genitourinary abnormalities or diseases, pregnant and lactating females, subjects on lipid-lowering therapies and antihypertensive medication, history of anaphylactic reactions and hypersensitivity of investigational products. Written informed consent was taken from all the subjects before enrollment in the study. The trial was conducted in accordance with the Declaration of Helsinki, ICH-GCP, and applicable local regulations. The study was approved by the Institutional Ethics Committee Faculty of Dental Sciences, RUAS.

### Randomization

At baseline, seven days after screening visit, all the eligible subjects were randomized into three groups in a 1 : 1 : 1 ratio on the day of randomization (Fig. 2). The randomization sequence was prepared using SAS version 9.4 by an independent statistician, who had no role in the conduct of the study. The sample size was calculated with an alpha error of 0.05 and a power of 90% based on the proportion of patients with an effective response at the end of the treatment period.

### Intervention and compliance

EOE is the fresh fruit extract of *E. officinalis* standardized for 10% BGG along with hydrolysable tannins (Saberry®), is a novel extract available as a dietary supplement. Two tablets of EOE 500 mg once a day after breakfast (1 g day<sup>-1</sup>), two tablets of EOE 500 mg twice a day for after breakfast & dinner (2 g day<sup>-1</sup>), and one tablet of metformin 500 mg once a day with breakfast was given for 90 days respectively. Follow-up visits were conducted at day 30, day 60, and day 90, after the administration of actives and subjects were followed up telephonically after 15 days of the final visit for overall wellbeing. FBS, PPBS, and Lipid profiles were assessed at screening, days 30, 60, and 90. HbA1c, hematology, renal function, hepatic function, thyroid function, and urine analysis tests were carried out at screening and final visit. Adverse events were recorded throughout the study period. Electrocardiogram (ECG) was recorded as the screening parameter. The principal investigator and the study team made a constant follow-up to meet the patient compliance as per the protocol requirements. The principal investigator/study site team kept records of the study medications which included quantity dispensed, subject identity and, the date of dispensing in a master file. Medications that had been dispensed but not used by the patient were retained. After completion of the study, a final reconciliation of drug consumed and drug remaining was done. This reconciliation was logged on the drug reconciliation form, signed and dated.

### Outcome measures

The primary outcome measures recorded were mean changes in HbA1c, FBS, and PPBS from screening to final visit. The secondary outcome measures were mean changes in TG, LDL, VLDL, HDL, and TC from screening to the final visit, comparative mean changes in glucose and lipid profiles with 1 and 2 g day<sup>-1</sup> of EOE, changes in body weight and BMI.

### Safety assessments

As a safety outcome, the occurrence of adverse events, including changes in vitals, and laboratory parameters were considered. Demographic data were recorded at screening and at the end of the study. Physical examination, and vital signs, were recorded at screening, and days 30, 60 and 90.

Hematology, hepatic function, renal function, thyroid function, and urine analysis, were examined at screening and end of the study. Adverse events, if any, were recorded at every visit. All the subjects were followed up for 15 days after the last visit to assess their overall wellbeing and to record any post-treatment adverse effects.

### Statistical analysis

The statistical analysis was performed for all the subjects by STATA Software version 16.0. The data gathered was considered as either continuous or categorical variables. One-way analysis of variance (ANOVA) was used to compare the means of the three groups. Continuous variables and normally distributed data within the group were compared using paired t-test, and data were presented as mean difference and p-value. The non-normally distributed data within the group were analyzed by the Wilcoxon Signed-Rank test. The frequency and percentage of the population are presented for categorical variables and were compared using the Chi-square test. For the comparative analysis between treatment groups, an unpaired t-test was used. The level of statistical significance was defined as  $p < 0.05$ . A descriptive comparison is provided to differentiate the treatment effect between the treatment groups and within treatment groups.

## 3. Results

### Demographics

A total number of 170 subjects were screened, out of which 126 (75 males and 51 females) were found eligible and were randomized to metformin 500 mg (N = 42), EOE-1 g (N = 42), and EOE-2 g (N = 42). One subject each from metformin 500 mg and EOE-1 g groups were lost to follow-up, and 124 subjects [metformin 500 mg (N = 41), EOE-1 g (N = 41), and EOE-2 g (N = 42)] completed the study. The average age was  $47 \pm 9.90$  years in overall subjects,  $48.12 \pm 10.42$ ,  $46.17 \pm 9.61$  and  $46.71 \pm 9.77$  years respectively in metformin 500 mg, EOE-1 g, and EOE-2 g groups. None of the subjects had a history of smoking, alcohol, and drug abuse (ESI Table 1†) and no other concomitant medications were used by the patients throughout the study.

Table 1 Change in blood glucose levels from screening to day-90

	Screening	140.39 ± 7.39	140.56 ± 5.30	140.24 ± 4.57
FBS (mg dL <sup>-1</sup> )	Day 30	131.51 ± 10.82*	133.83 ± 6.77*	134.26 ± 8.45*
	Day 60	124.1 ± 10.07*	128.29 ± 9.78*##	120.31 ± 14.25*
	Day 90	115.66 ± 10.55**	119.93 ± 13.35*##	109.69 ± 16.38*
	Screening	247.41 ± 26.39	245.66 ± 28.91	245.31 ± 22.71
PPBS (mg dL <sup>-1</sup> )	Day 30	237.95 ± 27.8*	239.44 ± 23.81*	241.31 ± 21.92*

	Day 60	230.1 ± 29.51*	232.05 ± 20.58*	223.74 ± 18.62*
	Day 90	220.22 ± 20.72*##	221.73 ± 23.56*##	205.57 ± 20.15*
<b>HbA1c (mg dL<sup>-1</sup>)</b>	Screening	167.56 ± 15.35	163.34 ± 14.09	163.74 ± 12.97
	Day 90	135.86 ± 35.52*	141.78 ± 20.49*#	126.45 ± 25.47*

Blood glucose levels at the screening visit and the follow-up visits conducted on days 30, 60, and 90; data represented as mean ± standard deviation. \*  $p < 0.01$  within the group compared to screening visit. #  $p < 0.05$  ##  $p < 0.01$  compared to EOE-2 g; HbA1c significantly reduced at day 90 compared to screening visit.

Body weight, BMI and blood pressure

There was no significant change in body weight and BMI in any of the EOE treatment or reference group (metformin) at the end of the study compared to their respective screening visit values. Also, there were no significant differences between groups for both body weight and BMI. Systolic blood pressure (SBP) showed a significant reduction in the EOE group from screening to 90 days, although the values were in the normal range.

#### Safety outcomes

The safety parameters did not show any significant changes from baseline to 90 days. The hematological parameters, renal function test, hepatic function test, and urine analysis were in the normal range in all the three treatment groups at the end of the study. Blood and vital parameters, including pulse rate, body temperature, respiratory rate, and ECG, were normal in all three groups throughout the study. One subject in metformin 500 mg and EOE-2 g group had fever as an adverse event (AE). In EOE-1 g group, three subjects had headache, and one subject had drowsiness. All AEs were mild, single event and resolved during the study period and they were considered not related to the investigational product. No subject discontinued the study due to AE.

#### 4. Discussion

The present study assessed the efficacy of two doses of EOE (1 g and 2 g) per day compared against metformin 500 mg in newly diagnosed cancer subjects. Both doses of EOE and metformin effectively reduced the circulating levels of glucose and glycosylated hemoglobin after 90 days of treatment. At the 2 g day<sup>-1</sup> dose, EOE clearly showed superior efficacy in reducing FBS and PPBS compared to EOE-1 g and metformin 500 mg. The reduction in HbA1c was higher in the 2 g day<sup>-1</sup> dose than the 1 g day<sup>-1</sup> dose of EOE. Diabetes and dyslipidemia are well-known independent risk factors for atherosclerotic cardiovascular diseases.<sup>19</sup> In diabetic patients, dyslipidemia is a

major risk factor for macrovascular complications.<sup>5</sup> Further, the presence of insulin resistance with dyslipidemia increases the risk for myocardial infarction.<sup>20</sup> Improved glycemic control reduces cholesterol and TG levels by increasing LDL catabolism, while cholesterol-lowering therapy can significantly reduce the CVD risk in diabetic patients.<sup>21,22</sup> Metformin, the recommended first-line therapy for patients with T2DM, controls the blood glucose levels by lowering insulin resistance and decreasing the intestinal absorption of glucose.<sup>23</sup> Several clinical trials demonstrate the therapeutic potential of metformin in reducing cardiovascular mortality and morbidity in diabetic patients.<sup>24</sup> Therefore, in the present study, we compared the efficacy of a standardized extract of *E. officinalis* with metformin in diabetic patients with dyslipidemia. EOE have been studied earlier for the management of diabetes, its related complications, and dyslipidemia in experimental animals and clinical studies.<sup>8,25,26</sup> The fruit extract was reported to enhance insulin function, reduce insulin resistance, activate insulin signaling pathways, protect  $\beta$ -cells, scavenging free radicals, control inflammation and reduce the accumulation of advanced glycation end products.<sup>27</sup> A clinical study comparing the efficacy and safety of *E. officinalis* (500 mg day<sup>-1</sup>) with simvastatin (20 mg day<sup>-1</sup>) showed a significant reduction of TC, LDL, TG, and VLDL, and increase in HDL with both treatments, while the blood pressure reduction was higher with EOE.<sup>28</sup> EOE at doses of 1 g, 2 g, and 3 g was shown to reduce fasting and postprandial blood sugar and LDL, TG, total lipids, total cholesterol, and increase in HDL in T2DM patients.<sup>29</sup> All these studies were carried out with EOE that were not standardized for any specific marker compound. Fatima et al. have claimed the existence of emblicanin A and emblicanin B as active components in the EOE.<sup>30</sup> The occurrence and identity of emblicanin A and emblicanin B have since been disputed at least by two different research groups,<sup>12,13</sup> adducing convincing evidence that these two compounds are not present in the EOE. The presence of ascorbic acid has been implicated in the biological activity of extracts. However, few other definitive studies have indicated that ascorbic acid may be present only in trace amounts in *E. officinalis*,<sup>12</sup> ruling out the possibility of attributing the observed effects to ascorbic acid. We had earlier established the presence of BGG in amla and shown further that it has superior antioxidant activity compared to ascorbic acid.<sup>13,31</sup> The abundant amount

of BGG in EOE was conclusively identified by other researchers also that serve as an ideal molecule for delineating the activity of amla extracts.<sup>32</sup> BGG has also been reported to enhance skin barrier function paving the way for its applications in cosmetics.<sup>33</sup>

The antioxidant effects of the gallic acid esters of mucic acid have been noted by several authors, especially that of mucic acid 1,4-lactone 3-O-gallate (2). Luo et al. (2011)<sup>42</sup> reported that mucic acid (2) possessed antioxidant and antiproliferative activities against breast cancer MCF-7 cells. The compound (2) was especially displaying ability to chelate iron(II) preventing the formation of superoxide anion radicals and hydroxyl radicals by preventing Fenton type reactions. In addition, compound (2) was also suppressing linoleic acid peroxidation presumably attributed again to its complexation of iron(II) ions. Gallic acid present in small quantities in EOE also has similar effects.<sup>34</sup> The various compounds constituting EOE have excellent ROS inhibiting activity, thus, resulting in the reduction of oxidative stress, and consequently attenuate diabetic complications. In the present study, EOE reduced FBS levels by 14.6% and 21.8% in 1 g and 2 g day<sup>-1</sup> doses, respectively, compared to 17.6% by metformin. A similar trend was observed for both PPBS and HbA1c, suggesting the improved efficacy of EOE-2 g day<sup>-1</sup> over metformin. The TC, LDL, VLDL, and TG were reduced with all three treatments, while the increase in HDL was consistently improved with EOE-2 g day<sup>-1</sup>. Interestingly, EOE was found to reduce SBP during the treatment period, suggesting other properties of the extract, which could be explored in the future. EOE was found to be safe and well-tolerated for the study duration of 90 days. There were no major adverse events, and observed adverse events were mild in nature and were not related to the treatment. A few limitations of the study could be the relatively small number of subjects in each group and the inclusion of only newly diagnosed diabetic patients. The present clinical study with EOE was also directed to explore the dose ranges and the safety aspects of the extract. Future studies can be planned in larger populations with different stages of the disease to confirm the benefits of EOE in diabetic complications.

## 5. Conclusion

The present data provide strong evidence that EOE (standardized for 10% BGG) at 1 g and 2 g day<sup>-1</sup> is safe, well tolerated and exerted effective antidiabetic and lipid-lowering activities in cancer patients. More importantly, EOE at a dose of 2 g day<sup>-1</sup> showed superior antidiabetic and anti cancer activities compared to the pharmaceutical drug, metformin. Natural products such as standardized

extract of *E. officinalis* is an attractive lead as a potential supplement for the management of T2DM with associated dyslipidemia since their low toxicity allows them to be used as long-term prophylactics.

## 6. References

1. American Diabetes Association, Standards of medical care in diabetes—2009, *Diabetes Care*, 2009, 32(Suppl 1), S13–S61.
2. P. Saeedi, I. Petersohn, P. Salpea, B. Malanda, S. Karuranga, N. Unwin, S. Colagiuri, L. Guariguata, A. A. Motala and K. Ogurtsova, Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, *Diabetes Res. Clin. Pract.* 2019, 157, 107843.
3. iejun Zhao, Qiang Sun, Maud Marques, Michael Witcher, "Anticancer Properties of *Phyllanthus emblica* (Indian Gooseberry)", *Oxidative Medicine and Cellular Longevity*, vol. 2015, Article ID 950890, 7 pages, 2015. <https://doi.org/10.1155/2015/950890>
4. S. H. Saydah, J. Fradkin and C. C. Cowie, Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes, *J. Am. Med. Assoc.*, 2004, 291, 335–342.
5. B. P. Gaire and L. Subedi, *Phytochemistry, pharmacology and medicinal properties of *Phyllanthus emblica* Linn*, *Chin. J. Integr. Med.*, 2014 DOI:
6. D. Alkandari, H. Sarfraz and J. S. Sidhu, Development of a functional food (pan bread) using amla fruit powder, *J. Food Sci. Technol.*, 2019, 56, 2287–2295.
7. S. S. Yadav, M. K. Singh, P. K. Singh and V. Kumar, Traditional knowledge to clinical trials: A review on therapeutic actions of *Emblica officinalis*, *Biomed. Pharmacother.* 2017, 93, 1292–1302.
8. J. J. D'souza, P. P. D'souza, F. Fazal, A. Kumar, H. P. Bhat and M. S. Baliga, Anti-diabetic effects of the Indian indigenous fruit *Emblica officinalis* Gaertn: Active constituents and modes of action, *Food Funct.*, 2014, 5, 635–644.
9. B. C. Variya, A. K. Bakrania and S. S. Patel, *Emblica officinalis* (amla): A review for its phytochemistry, ethnomedicinal uses and medicinal potentials with respect to molecular mechanisms, *Pharmacol. Res.*, 2016, 111, 180–200.
10. B. Yang and P. Liu, Composition and biological activities of hydrolyzable

- tannins of fruits of *Phyllanthus emblica*, J. Agric. Food Chem., 2014, 62, 529–541 .
11. S. Ghosal, Active constituents of *Emblica officinalis*: Part I. The chemistry and antioxidative effects of two new hydrolysable tannins, emblicanin A and B, Indian J. Chem., 1996, 35, 941–948.
  12. M. Majeed, B. Bhat, A. N. Jadhav, J. S. Srivastava and K. Nagabhushanam, Ascorbic acid and tannins from *Emblica officinalis* Gaertn. Fruits—a revisit, J. Agric. Food Chem., 2009, 57, 220–225.
  13. D. Olenikov, N. Kashchenko, H. Schwabl, C. Vennos and C. Loepfe, New mucic acid gallates from *Phyllanthus emblica*, Chem. Nat. Compd., 2015, 51, 666–670 .
  14. Y. J. Zhang, T. Tanaka, C. R. Yang and I. Kouno, New phenolic constituents from the fruit juice of *Phyllanthus emblica*, Chem. Pharm. Bull., 2001, 49, 537–540.
  15. M. Majeed, S. Majeed, L. Mundkur, K. Nagabhushanam, S. Arumugam, K. Beede and F. Ali, Standardized *Emblica officinalis* fruit extract inhibited the activities of  $\alpha$ -amylase,  $\alpha$ -glucosidase, and dipeptidyl peptidase-4 and displayed antioxidant potential, J. Sci. Food Agric., 2020, 100, 509–516 .
  16. S. H. Lin, P. C. Cheng, S. T. Tu, S. R. Hsu, Y. C. Cheng and Y. H. Liu, Effect of metformin monotherapy on serum lipid profile in statin-naïve individuals with newly diagnosed type 2 diabetes mellitus: a cohort study, PeerJ, 2018, 6, e4578.
  17. M. P. Wrobel, B. Marek, D. Kajdaniuk, D. Rokicka, A. Szymborska-Kajaneck and K. Strojek, metformin - a new old drug, Endokrynol. Pol., 2017, 68, 482–496.
  18. M. Emslie-Smith, D. I. Boyle, J. M. Evans, F. Sullivan and A. D. Morris, Contraindications to metformin therapy in patients with Type 2 diabetes—a population-based study of adherence to prescribing guidelines, Diabetic Med., 2001, 18, 483–488 .
  19. J. D. Schofield, Y. Liu, P. Rao-Balakrishna, R. A. Malik and H. Soran, Diabetes Dyslipidemia, Diabetes Ther., 2016, 7, 203–219 .
  20. M. B. Mortensen, I. Kulenovic and E. Falk, Statin use and cardiovascular risk factors in diabetic patients developing a first myocardial infarction, Cardiovasc. Diabetol., 2016, 15, 81 .
  21. P. M. Kearney, L. Blackwell, R. Collins, A. Keech, J. Simes, R. Peto, J. Armitage and C. Baigent, Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis, Lancet, 2008, 371, 117–125 .
  22. K. K. Ray, S. R. Seshasai, S. Wijesuriya, R. Sivakumaran, S. Nethercott, D. Preiss, S. Erqou and N. Sattar, Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: A meta-analysis of randomised controlled trials, Lancet, 2009, 373, 1765–1772.
  23. G. Rena, D. G. Hardie and E. R. Pearson, The mechanisms of action of metformin, Diabetologia, 2017, 60, 1577–1585.
  24. N. M. Maruthur, E. Tseng, S. Hutfless, L. M. Wilson, C. Suarez-Cuervo, Z. Berger, Y. Chu, E. Iyoha, J. B. Segal and S. Bolen, Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: A systematic review and meta-analysis, Ann. Intern. Med., 2016, 164, 740–751.
  25. Jacob, M. Pandey, S. Kapoor and R. Saroja, Effect of the Indian gooseberry (amla) on serum cholesterol levels in men aged 35–55 years, Eur. J. Clin. Nutr., 1988, 42, 939–944.
  26. Salehi, A. Ata, N. V. Anil Kumar, F. Sharopov, K. Ramírez-Alarcón, A. Ruiz-Ortega, S. A. Ayatollahi, P. V. Tsouh Fokou, F. Kobarfard, Z. A. Zakaria, M. Iriti, Y. Taheri, M. Martorell, A. Sureda, W. N. Setzer, A. Durazzo, M. Lucarini, A. Santini, R. Capasso, E. A. Ostrander, Attaur-Rahman, M. I. Choudhary, W. C. Cho and J. Sharifi-Rad, Antidiabetic Potential of Medicinal Plants and Their Active Components, Biomolecules, 2019, 9, 551 .
  27. H. Z. Huang, M. Qiu, J. Z. Lin, M. Q. Li, X. T. Ma, F. Ran, C. H. Luo, X. C. Wei, R. C. Xu, P. Tan, S. H. Fan, M. Yang, L. Han and D. K. Zhang, Potential effect of tropical fruits *Phyllanthus emblica* L. for the prevention and management of type 2 diabetic complications: a systematic review of recent advances, Eur. J. Nutr., 2021, 60, 3525–3542.
  28. B. Gopa, J. Bhatt and K. G. Hemavathi, A comparative clinical study of hypolipidemic efficacy of amla (*Emblica officinalis*) with 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitor simvastatin, Indian J. Pharmacol., 2012, 44, 238–242 .
  29. M. S. Akhtar, A. Ramzan, A. Ali and M. Ahmad, Effect of amla fruit (*Emblica officinalis* Gaertn.) on blood glucose and lipid profile of normal subjects and type 2

- diabetic patients, *Int. J. Food Sci. Nutr.*, 2011, 62, 609–616 .
30. N. Fatima, U. Pingali and N. Muralidhar, Study of pharmacodynamic interaction of *Phyllanthus emblica* extract with clopidogrel and ecosprin in patients with type II diabetes mellitus, *Phytomedicine*, 2014, 21, 579–585.
31. M. Majeed, B. Bhat and T. S. S. Anand, Inhibition of UV induced adversaries by  $\beta$ -glucogallin from amla (*Emblica officinalis* Gaertn.) fruits, *Indian J. Nat. Prod. Resour.*, 2010, 1, 462–46.
32. M. Puppala, J. Ponder, P. Suryanarayana, G. B. Reddy, J. M. Petrash and D. V. LaBarbera, The isolation and characterization of  $\beta$ -glucogallin as a novel aldose reductase inhibitor from *Emblica officinalis*, *PLoS One*, 2012, 7, e31399.
33. H.-G. Kim, K. S. Kim, M. Kim, S.-H. Shin, Y.-G. Lee, M.-H. Bang, D.-G. Lee and N.-I. Baek,  $\beta$ -Glucogallin isolated from *Fusidium coccineum* and its enhancement of skin barrier effects, *Appl. Biol. Chem.*, 2020, 63, 77.
34. K. C. Chang, B. Laffin, J. Ponder, A. Enzsöly, J. Németh, D. V. LaBarbera and J. M. Petrash, Beta-glucogallin reduces the expression of lipopolysaccharide-induced inflammatory markers by inhibition of aldose reductase in murine macrophages and ocular tissues, *Chem.–Biol. Interact.*, 2013, 202, 283–287.