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APPLE SEEDS: PHYTOCHEMISTRY, MEDICINAL PROPERTY AND TOXICOLOGY

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ABSTRACT: People throughout the world have long used various fruits, leaves, and plant parts as nutraceuticals and valuable sources of herbal treatments. Apples (*Malus domestica*) are a popular fruit with a high level of medicinal efficacy, whose seeds have also demonstrated a very high therapeutic and nutritional value when ingested in the right amount and form (apple seed flour or oil). Found in cold temperate regions worldwide and in the states of Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Uttar Pradesh and Arunachal Pradesh in India. *Malus domestica* fruit, peels and seeds, when extracted in alcohol or acetone medium, show a high content of proteins, fatty acids, dietary fibres, polyphenols, vitamins and minerals, polysaccharides, phytosterols, pentacyclic triterpenes and cyanogenic glycosides (amygdalin). Polyphenols like proanthocyannidin, catechin, quercetin, phloridzin are very effective in treating hyperglycemia, cholesterol, neuropsychiatric diseases, cancer, and gastrointestinal disorders. Another cytotoxic component present in the seeds is amygdalin, which shows anti-proliferative and anti-inflammatory properties. Other than this, pectin, a polysaccharide (peel and seeds), phytosterols (leaves, stem, root, seeds), pentacyclic triterpenes (peel and seeds), along with other mentioned constituents, show high antioxidant, anti-obesity, anti-viral, anti-proliferative, anti-microbial, anti-diabetic, anti-depressant, anti-inflammatory, anti-ageing and immunity-boosting activity. This review provides the prospect of utilizing mainly the seeds that are generally considered to be "waste" of this deciduous tree *Malus domestica* fruit, showing immense phytochemical components with lots of medicinal values, and thus provides new scope for utilizing its chemical constituents in herbal drug design shortly to treat acute and chronic diseases.

INTRODUCTION: Gradually, with time and discoveries of inorganically synthesized chemical drugs, herbal medicines have created a new horizon in treating some of the most common chronic and critical diseases over decades. Due to very low or negligible side effects, most people prefer medicines obtained from plants, leaves, fruits, or seed extracts in the present era.

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Nowadays, above 75% of the worldwide population prefers herbal medicines and focuses on proper nutrition, leading to several new studies and research in this field of organically or herbally synthesized drugs and nutraceuticals. Apple (*Malus domestica*), a very common fruit, has shown several medicinal properties, including anti-proliferative action, as stated in the phrase "An apple a day keeps the doctor away" by the ancient physician Hippocrates [1].

Found throughout the temperate zones, it is most likely grown in countries like China, India and Brazil. "Malus", the Latin word that means "evil or apple" and "domestica" is the feminine nominative of "domesticus".

Deciduous in nature, cultivated trees are 2 to 4.5m with dark green alternately arranged oval leaves and serrated margins. Blooming during spring, it produces white five-petaled blossoms of 3-4cm with pinkish shades and inflorescence comprising of a cyme having 4-6 flowers with a central flower called "King Bloom". Fruit is fleshy with sizes ranging from 5-9cm in diameter with different colours like red, green, yellowish-red, *etc*. There are five carpels at the center of the fruit, each carpel containing 2-3 seeds. Each seed is small oval-shaped, black in colour, 0.3 inch long, 1/4th inch wide, about 1/8th inches thick, and mildly toxic [2, 3, 4].

Bioactive components like flavonoids, polyphenols, pentacyclic triterpenes, dihydrochalcones, polysaccharides, and a good quantity of proteins, lipids, and dietary fibers, and trace amounts of vitamins and minerals are obtained from different parts of the fruit [5, 6, 7]. Medical conditions like diabetes (mainly type II), obesity, neuropsychiatric disorders, several microbial and bacterial infections, inflammatory diseases and ulcers, digestive problems, coronary heart diseases, chronic bronchitis and even cancer [8] can be prevented by proper consumption of this fruit. Hep-2 liver cancer cells and Caco-2 colon cancer cells have shown inhibition of cell proliferation when used in a specific and regular dosage due to unique phytochemical composition (found mainly in the apple peel and seeds) [2].

Apple seeds are rich in protein (38.5%) and fat content showing oleic acid (46.5%) and linoleic acid (43.81%). With better stability, apple seed oils can be used as an edible oil with high iodine and saponification values. Moreover, the antioxidant capacity (IC_{50}) being ~40.06 µg/mL have proved to be a good source of natural antioxidant. The cytotoxic activity of apple seed oil has proved to be preventive against the human cervical cancer cell and lung carcinoma [9, 10, 11].

Apple juice or apple extract has a variety of uses for manufacturing fragrances, can be used as a blood pressure controlling agent, anti-aging nutritional products, and improving growth and skin texture quality [5]. In addition, it increases memory by inducing the effect of the neurotransmitter Acetyl-CoA [2].

This article aims to put up the morphology, phytochemical and pharmacological properties, and toxicity of *Malus domestica* fruit and its seed to give systemic and adequate information about it in the field of herbal medicinal research.

Literature Review:

Taxonomical Classification [6]:

Domain: Eukaryota

Kingdom: Plantae

Phylum: Spermatophyta

Subphylum: Angiospermae

Class: Dicotyledonae

Order: Rosales

Family: Rosaceae (Rose family)

Genus: Malus

Species: *M. domestica*

Binomial Name: *Malus domestica*

Synonyms in Different Languages [2]:

English: Apple

Gujrati: Safarjan

Hindi: Oriya Sev

Kannada: Sebu

Kashmiri: Tsoonth

Marathi: Safar Chad

Malayalam: Epal

Origin and Distribution: The apple tree is found mainly in the cool temperate zones of latitudes ranging from 35-50 degrees worldwide. Primary production is from China [6], while India follows next.

Regions of Jammu & Kashmir, portions of Himachal Pradesh, and hilly slopes of Uttar Pradesh and Uttaranchal favour bulk apple production in India, along with some parts of Arunachal Pradesh **Fig. 1.**

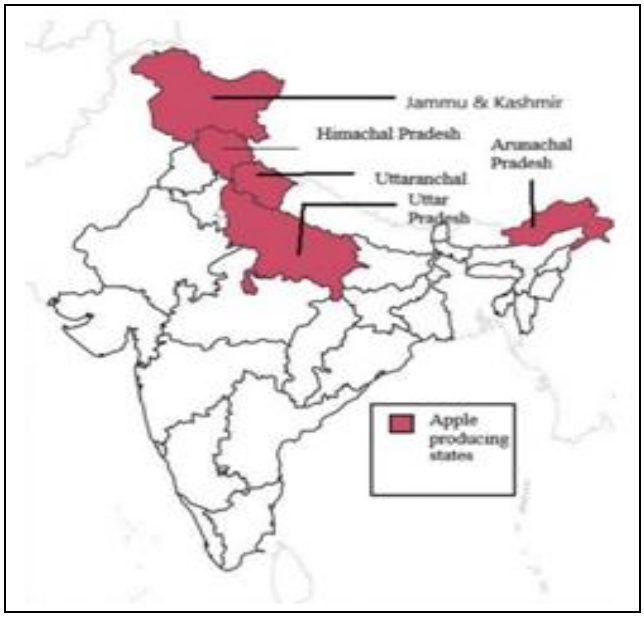

FIG. 1: INDIA MAP SHOWING STATES WHERE APPLES ARE GROWN

Cultivation: Kashmir and Himachal Pradesh Apples are cultivated in upper hilly terrains at an altitude of 1600-2500m above sea level. They are harvested during late August as they require an adequately chilled climate for production, except for the species grown in the Nilgiris that are harvested from April to July. A period of 130-150 days is required after complete blooming[7].

Botanical Morphology: Growing in cool temperate zones, apple trees are adaptive to several climates and soil conditions, but they preferably grow in loamy, well-drained, deep soil (45 cm depth) with pH varying between 5.5-6.5 and receiving rainfall of 1000-1250 mm and having a summer temperature around 21-24°C during the active growing period. Apple trees are deciduous, have grey-brown bark all over the trunk, and branches are reddish-brown and have ovate, dark-green leaves with asymmetrical leaf bases with curved and serrated leaf margins [7].

Flower: The monoecious plant has white or pinkish-white blossoms produced during spring with an approximate size of 3-4 cm and 5 petals. It is an inflorescence consisting of a cyme with 4-6 flowers, with "King Bloom" being the central flower [4].

Fruit: Each fruit is generally 7-8.5cm in diameter that matures typically during late summer to autumn with different colours of their peel varying from red, green, yellow or pink with a protective layer of epicuticular wax and the flesh being pale-yellow or pinkish yellow **Fig. 2** [2,4].

Seed: Oval-shaped, dark-brown seeds, present at the centre of the fruit having five carpels and each carpel containing 2-3 seeds of length varying from 7.69mm (GD) to 9.43mm (RD), width 4.02mm (GD) to 4.87mm (RD) ad thickness range of 2.01mm (RD) to 2.03mm (GD) having strong seed coat protecting the embryo **Fig. 2** [2] internally.

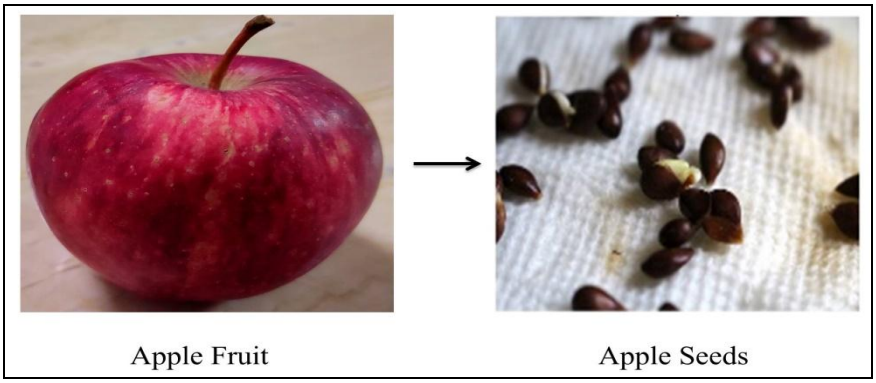

FIG. 2: PICTURE OF FRESH APPLE FRUIT ALONG WITH SEEDS

Proximate Composition of Apple Seeds: The proximate composition of apple seeds has been represented pictorially below **Fig. 3**. It shows the highest content of crude protein% (~34.0±0.5), followed by corresponding crude fat % (~27.7±0.7), carbohydrate% (~24±1.9), moisture% (~10.2±0.4) and negligible quantity of ash % (~4.1±0.3) **Fig. 3** [4].

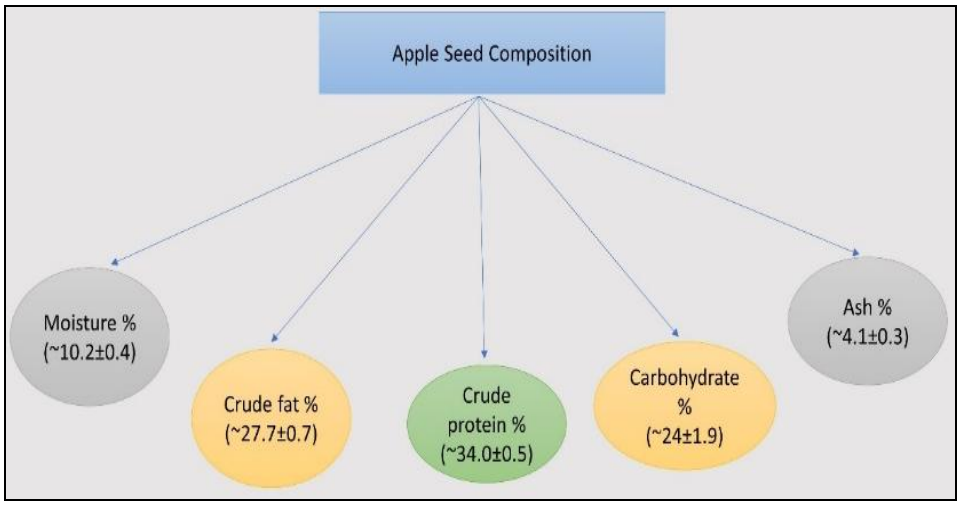

FIG. 3: SCHEMATIC REPRESENTATION SHOWING PROXIMATE COMPOSITION OF APPLE SEEDS

Phytochemical Composition of Apple Seeds: Research articles on the phytochemical composition of apple seeds have obtained several data **Fig. 3** and the constituents effective in exhibiting antioxidant, anti-bacterial, anti-depressant, anti-proliferative, anti-diabetic, anti-obesity and anti-inflammatory properties. The apple seeds extracted by n-hexane and then dried and correspondingly dissolved in 80% methanol have reported the presence of high content of proteins (49.5g/100g) [predominantly glycine, arginine, moderate quantity of leucine and trace amount of methionine and moderate or minor amounts of other amino acids], fatty acids (24g/100g) [saturated and unsaturated fatty acids, linoleic acid, oleic acid, palmitic and stearic acid], dietary fibers [soluble (1.79%) and insoluble (1.39%)] and high quantity phenolic compounds [12.30±0.96mg GAE/g DW(RD) and 7.17±0.47mg GAE/g DW(GD)]. But some other studies have shown that the total quantity of polyphenolic compounds reported in the case of acetone extract was of higher value, i.e., 2 to 16mg GAE/g **Fig. 5** [4, 8].

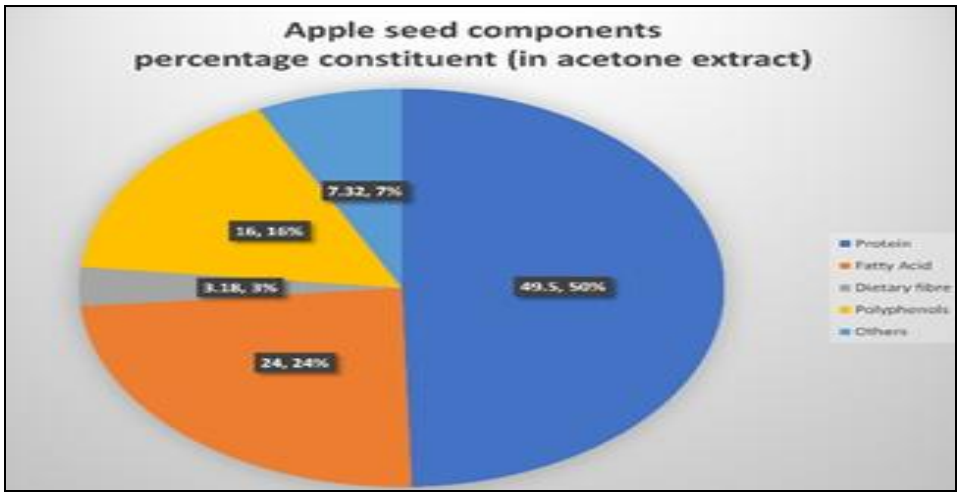

FIG. 4: PERCENTAGE CONSTITUENT OF APPLE SEED COMPONENTS

The main polyphenolic components as obtained from several studies have shown presence of hydroxycinnamic acid (chlorogenic acid), dihydrochalcones (phloridzin) and flavonoids [flavonols (quercetin), flavon-3-ols (catechin, epicatechin), proanthocyanidins] **Fig. 5** [9-12].

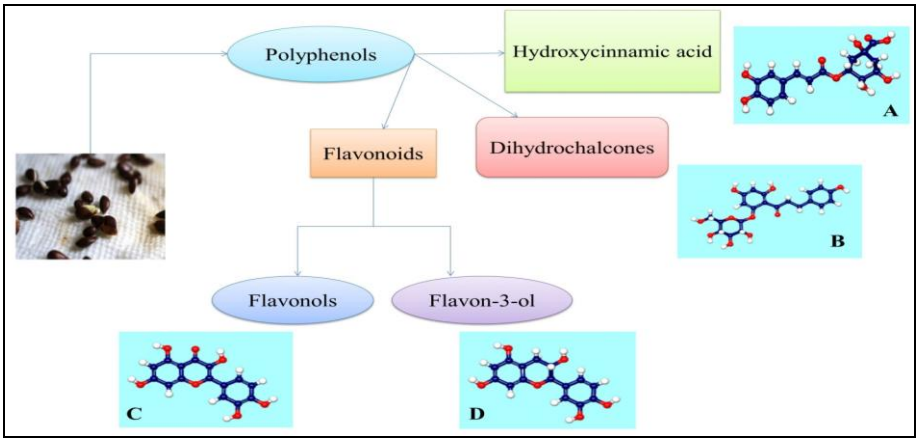

FIG. 5: SCHEMATIC REPRESENTATION OF TYPES OF POLYPHENOLS IN APPLE SEEDS AND THEIR 3D CHEMICAL STRUCTURES [A: CHLOROGENIC ACID; B: PHLORIDZIN; C: QUERCETIN; D: CATECHIN]

Other than polyphenols, apple seeds also contain certain amounts of polysaccharides (pectin) [higher content in the peel of apples] **Fig. 6A**, phytosterols (sitosterol, daucosterol) **Fig. 6B** and a trace amount of pentacyclic triterpenes (triterpenic acid, ursolic acid) **Fig. 6C** [also found in apple peels] [5, 8, 13, 14].

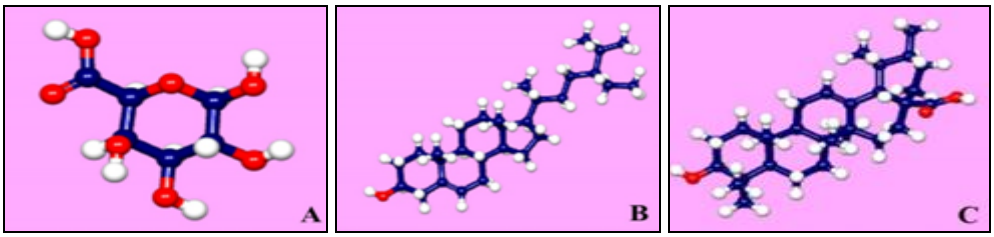

FIG. 6: DIFFERENT CHEMICAL STRUCTURES IN THEIR 3D FORMAT [A: PECTIN; B: SITOSTEROL; C: URSOLIC ACID]

Another very important compound in apple seeds is cyanogenic glycosides (amygdalin) **Fig. 7**, which also shows an anti-proliferative property in cells [15]. Some minerals like potassium, phosphorus, zinc, *etc*., present in the seeds also help develop and maintain body immunity [4]. All the chemical structures are downloaded from the PubChem database and converted to 3D format using Discovery Studio Visualizer 2020.

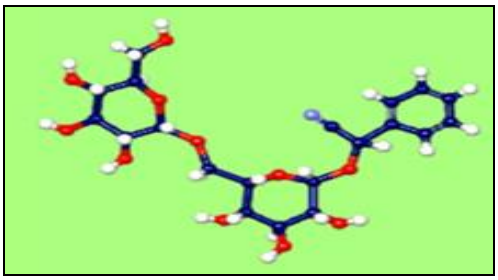

FIG. 7: 3D STRUCTURE OF AMYGDALIN

Sl. no.	Phytochemical components	Distribution	Therapeutic value
1.	Proteins	Pulp, seed	Promotes body growth and repairs tissues to help regulate blood sugar levels
2.	Fatty acids	Seed, pulp	Treats hyperpigmented skin and improves acne.
3.	Polyphenols and antioxidants	Seed, pulp, peel	Anti-inflammatory, anti-cancerous, helps to fight against cardiovascular diseases, anti-obesity, anti-bacterial, and anti-depressant
4.	Dietary fibres	Peel, seeds, flesh	Anti-diabetic helps keep bowel clear.
5.	Polysaccharides	Peel, seed, root, leaf, stem	Anti-tumour, anti-obesity, anti-viral, hemostatic effect
6.	Phytosterols	Peel, seed, stem, leaf, root	Anti-cancerous, anti-inflammatory
7.	Pentacyclictriterpenes	Peel and negligible in seeds	The cytotoxic effect has anti-tumour properties, anti-proliferative, and anti- depressant[8]
8.	Carbohydrates	Seed, pulp, leaf	An instant energy source for the brain and muscles.
9.	Vitamins and Minerals	Pulp, seed and peel	Antioxidants, pernicious anaemia and anti-ageing effect enhance immunity

Pharmacological and Therapeutic Effects: The whole of *Malus domestica* fruit, including seeds, have very effective phytopharmacological effects. The presence of several bioactive components is the main reason behind these effects and is represented pictorially below **Fig. 8.**

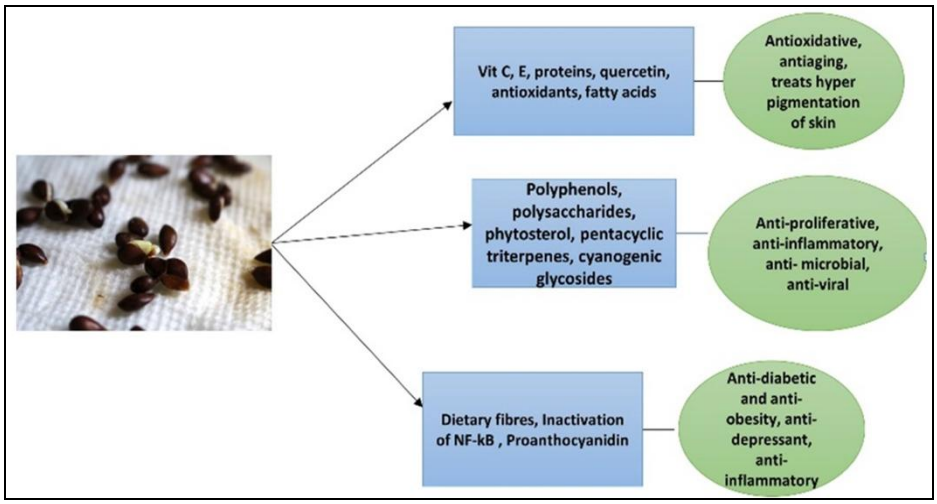

FIG. 8: SCHEMATIC REPRESENTATION OF SEVERAL PHARMACOLOGICAL EFFECTS DUE TO THE PRESENCE OF PHYTOCHEMICAL COMPONENTS IN APPLE SEEDS

Antioxidant Properties: Recent interest worldwide is emphasizing antioxidants obtained from natural sources of plants. *Malus domestic* flesh, peel, and seeds contain numerous vitamins C, E, and minerals and quercetin, a flavonol that makes it a rich source of antioxidants, showing an antioxidant capacity (IC_{50}) of 40µg/mL. It has been reported that 100gm apple provides 5.7mg approx of vitamin C [16-19]. This helps in preventing pernicious anaemia, enhances immunity, rejuvenates skin and provides anti-aging effects. High antioxidant has also decreased the chance of cardiovascular diseases and helped in sleep [2, 5, 6, 10, 11, 17, 18].

Anti-diabetic Properties: The presence of polyphenols like proanthocyanidins (flavonoids), quercetin (flavonols), and phloridzin (dihydrochalcones) in different fruit parts and seeds have helped in the inhibition of α-glycosidase thus reducing the chance of postprandial hyperglycemia (type II diabetes). Studies showed that proanthocyanidins are the most potent polyphenolic compound showing more than ~90% inhibition of α-glycosidase [2, 6, 16, 18].

Anti-obesity Properties: *M. domestica* pulp, peel, and especially seeds contain high proanthocyanidin, quercetin, and several triterpenes along with dietary fibres that have helped in oxidating the lipoprotein cholesterol and thus causing hypocholesterolemic mechanism. This helps decrease hepatic cholesterol levels and prevent fats deposition in cardiovascular tissues by keeping the heart and liver healthy [2, 5, 17, 18, 20].

Anti-proliferative Properties: Polyphenols, polysaccharides, phytosterols, pentacyclic triterpenes and mainly cyanogenic glycoside (amygdalin) present in different parts of the *Malus domestica* plant part, including the seeds, have shown effective in preventing some very common cancers like Hep-2 liver cancer and Caco-2 colon cancer by inhibiting type 2 glucose transporter (GLUT 2) [5, 7, 9, 11]. Colorectal cancer (CRC) prevention was reported due to the cause of change in polysaccharide components that modified the LPS/TLR4/NF-Kb pathway [LPS–lipopoly saccharide; TLR-4- Toll-like receptor 4; NF-kB-nuclear factor-kB] was observed due to change and breast cancer cell MCF-7 [3, 13, 15, 16]. The cyanogenic glycoside (amygdalin), being cytotoxic, exhibits major effectiveness in preventing the proliferation of malignant cells. This also provides hope in treating human cervical cancer, lung carcinoma, and skin cancer [18, 20].

Anti-microbial Properties: The phenolic components obtained from water and alcoholic apple fruit extracts and seeds have proved effective in preventing bacterial growth of gram-positive and gram-negative bacteria like *S. aureus* and *E. coli*,

respectively, and this has shown a future prospect in food manufacturing and cosmetic industries [16, 21, 22].

Anti-inflammatory Properties: Prevention of damage to gastrointestinal tissues as observed by polyphenol compounds and inactivation of NF-kB has resulted in anti-inflammatory activities of *M. domestica* fruit parts and seeds [2, 3, 5, 12].

Anti-depressant Properties: A good memory, effective sleep, and stable psychological state are mainly maintained due to the antioxidant, vitamin C, and polyphenolic contents of apple and its seeds. Acetyl -CoA, an important neurotransmitter of the human brain, is synthesized at a good rate due to these chemical compounds [2, 5].

Toxicological Effects: *Malus domestica* seeds contain cytotoxic properties due to the presence of amygdalin (1-4mg/g of apple seeds). This cyanogenic glycoside apparently can be very effective in preventing different types of malignancy when used in the form of apple seed oil or extracted properly [21, 22].

The seeds ingested intact do not cause toxicity, but if chewed in a certain quantity can be highly poisonous due to the formation of hydrogen cyanide (HCN) by undergoing metabolic reaction in the human body **Fig. 9** that can cause death when administered in lethal dose, *i.e.*, 50-300mg.

Comparative studies show other fruit parts containing several bioactive components are safe and provide high nutritional values and thus help prevent chronic diseases to a satisfactory extent [20, 22].

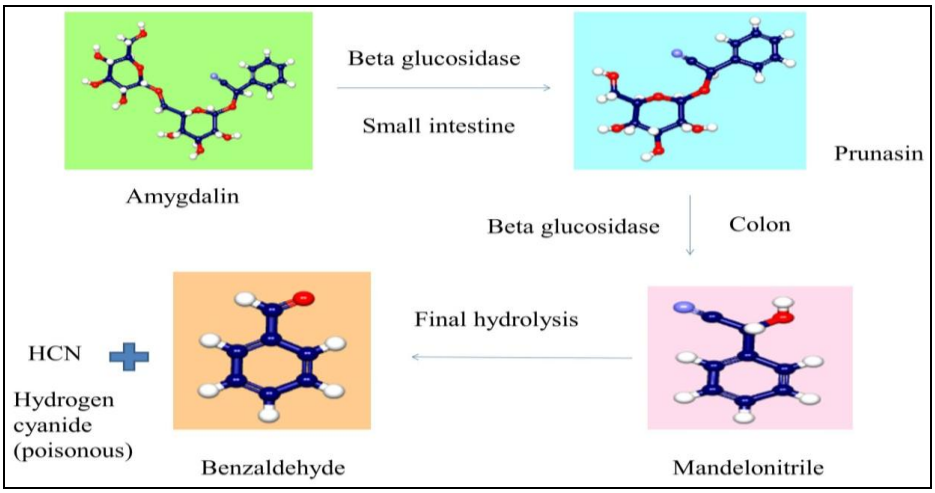

FIG. 9: FORMATION OF POISONOUS HCN FROM AMYGDALIN VIA METABOLIC PATHWAY IN MAMMALS

CONCLUSION: Scientific research and studies suggest the regular intake of apple and apple seed edible oil can positively impact the prevention of several health conditions through nutraceutical or therapeutic effects. The obtained phytochemicals or bioactive components and crude extracts can improve food products' quality and nutritional value. More research and studies on phyto-pharmacological ailments should be conducted in depth to implement the medicinal properties of the different *Malus domestica* plant parts in herbal drug designs worldwide and minimize the toxic effects. A vivid description of botanical morphology, bioactive, phytochemical ingredients, and medicinal and therapeutic effects of the fruit and its parts, including seeds, have been provided in this article. The use of the fruit and its parts as a herbal and nutritional supplement is accurate worldwide. Phytochemically active herbal ingredients and nanoencapsulation of active components using sustainable and biocompatible polymers provide a promising step in the world of herbal therapy in the near future.

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REFERENCES:

1. Spengler RN: Origins of the apple: The role of megafaunal mutualism in the domestication of Malus and rosaceous trees. Front Plant Sci 2019; 10: 617.
2. Lobo AR, Satish S and Shabaraya AR: Review on pharmacological activties of *Malus domestica*. Int J Pharm Chem Res 2018; 4: 243–246
3. Nezbedova L, McGhie T, Christensen M, Heyes J, Nasef NA and Mehta S: Onco-preventive and Chemo-preventive Effects of Apple Bioactive Compounds Nutrients. 2021; 13(11): 4025
4. Madrera RR and Valles SB: Characterization of Apple seeds and their oils from the cider-making industry; European Food Research and Technology 2018; 244: 1821-1827.
5. Jiri Patocka, Kanchan Bhardwaj, BlankaKlimova, Eugenie Nepovimova, Qinghua Wu, Marco Landi, KamilKuca, Martin Valis and Wenda Wu: *Malus domestica*: A Review on Nutritional Features, Chemical Composition, Traditional and Medicinal Value; Plants (2020); 9, 1408.
6. Azizah PN, Husnunnisa and Misfadhila S: Review of phytochemical and pharmacological effects of apple. International Journal of Research and Review 2020; 7(9): 231-237.
7. Mehnigar Hamid, Hassan GI, AbWaheedWani, Shahida Ashraf, SumayaMumtaz ShabnumAhad and M. YounusWani and Amit Kumar: Physiology of Flowering in Apple and Almond: A Review International Journal of Current Microbiology and Applied Science 2020; 9(9): 1912-1929.
8. Opyd P, Jurgo´nski A, Ju´skiewicz J, Milala J, Zdu´nczyk Z & Kr´ol B: Nutritional and health-related effects of a diet containing apple seed meal in rats. The case of amygdalin. Nutrients 2017; 9(10): 1091.
9. Jimnez BC, Vargas OLT and Garcia MER: Physicochemical characterization of quinoa (*Chenopodium quinoa*) flour and isolated starch. Food Chemistry 2019; 298: 124982.
10. Zhao T, Sun L, Wang Z, Nisar T, Gong T and Li D: The antioxidant property and α-amylase inhibition activity of young apple polyphenols are related with apple varieties. Lebensmittel-Wissenschaft und -Technologie- Food Science and Technology 2019; 111: 252–259.
11. Nile SH, Nile A, Liua J, Kim DH and Kai G: Exploitation of apple pomace towards extraction of triterpenic acids, antioxidant potential, cytotoxiceffects, and inhibition of clinically important enzymes. Food and Chemical Toxicology 2019; 131: 1-8.
12. Zhao S, Yang F, Liu Y, Sun D, Xiu Z, Ma X, Zhang Y and Sun G: Study of chemical characteristics, gelation properties and biological application of calcium pectate prepared using apple or citrus pectin.; Int. J. Biol. Macromol 2018; 109: 180–187.
13. Skinner RC, Gigliotti JC, Ku KM and Tou JC: A comprehensive analysis of the composition, health benefits and safety of apple pomace. Nutr Rev 2018; 76: 893–909.
14. Lobo AR, Satish S and Shabaraya AR: Review on pharmacological activties of *Malus domestica*. Int J Pharm Chem. Res 2018; 4: 243–246.
15. Tu SH, Chen LC and Ho YS: An apple a day to prevent cancer formation: Reducing cancer risk with flavonoids. J Food Drug Ana 2017; 25: 119–124.
16. Richardson AT, Cho J, McGhie TK, Larsen DS, Schaffer RJ, Espley RV and Perry NB: Discovery of a stable vitamin C glycoside in crab apples (*Malus sylvestris*). Phytochemistry 2020; 173: 112297.
17. Zielinska D, Laparra-Llopis JM, Zielinski H, Szawara-Nowak D and Giménez-Bastida JA: Role of apple phytochemicals, phloretin and phloridzin, in modulating processes related to intestinal inflammation. Nutrients 2019; 11: 1173.
18. Mehnaza Manzoor, Jagmohan Singh and Adil Gani: Characterization of apple (Malusdomestica) seed flour for its structural and nutraceutical potential; LWT - Food Science and Technology 2021; 151:112138.
19. Gunes R, Palabiyik I, Toker OS, Konar N and Kurultay S: Incorporation of defatted apple seeds in chewing gum system and phloridzin dissolution kinetics. Journal of Food Engineering 2019; 255: 9–14.
20. Ci Z, Kikuchi K, Hatsuzawa A, Nakai A, Jiang C and Itadani A: Antioxidant activity and α-glucosidase, α-amylase and lipase inhibitory activity of polyphenols in flesh, peel, core and seed from mini apple. American J of Food Science and Technology 2018; 6(6): 258–262.
21. Oduwole I and Abdelsnaser A: Amygdalin- Therapeutic Effects and Toxicity. Journal of Biotechnology and Biomedicine 2020; 3(2): 039-049.
22. Wojdylo A and Oszmianski J: Antioxidant Activity Modulated by Polyphenol Contents in Apple and Leaves during Fruit Development and Ripening. Antioxidants 2020; 9; 567.

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