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REVIEW ARTICLE

THERAPEUTIC BIOLOGICAL ACTIVITIES OF *Balanites aegyptiaca* (L.) Delile: A REVIEW

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ABSTRACT

Medicinal plants continue to be a crucial source of safe, less toxic, economical, available, and reliable natural medicine supplies all over the world. *Balanites aegyptiaca* Del. (Zygophyllaceae), commonly known as the "desert date", is a thorny shrub or tree found in arid parts of Africa and South Asia. It has traditionally been used to cure a variety of maladies such as wounds, haemorrhoids, jaundice, syphilis, intestinal worm infection, malaria, dysentery, constipation, diarrhoea, stomachaches, asthma, and fever. The fruits of *B. aegyptiaca* are highly effective as antioxidants, anti-inflammatory, antibacterial, antifungal, antiparasitic, antidiabetic, and anticancer. However, the safety and effectiveness of *B. aegyptiaca* have not been completely studied in humans, so additional well-planned clinical trials are required to corroborate preclinical findings. The WHO has stressed on continued research on medical plants since products derived from plants will continue to be in demand. Searches were conducted on Google Scholar, Science Direct, Google.com, Wiley, PubMed, Hindawi, Springer, and other relevant databases for research publications on *B. aegyptiaca*. Duplicate publications including thesis papers, and reviews of *B. aegyptiaca* were excluded This review presents a thorough overview of current information on the therapeutic characteristics of *B. aegyptiaca* with a focus on its biological activities. It briefly examines its traditional usage, taxonomy, and biological evaluation.

Keywords: Antidiabetic, *Balanites aegyptiaca*, cancer, diabetes, plant extract

1. INTRODUCTION

Plant remedies have been used for the treatment of numerous diseases for over 4,000 years because they contain beneficial chemical components. The primary therapeutic benefits of plants are derived from their phytochemical constituents, which, when given to humans, have a particular pharmacological impact. In medicinal plants, specialized phytochemicals are naturally present in

leaves, stem, roots, fruits, seeds that have their own defense mechanisms and protective ions from many illnesses. There has been a boom in interest in medicinal plants' therapeutic properties. *Balanites aegyptiaca* (L.) Delile is one of the most prevalent but underestimated wild plant species in Africa and South Asia. It is ubiquitous because it does well in a variety of soil types (from sand to clay) and levels of wetness. It can endure fire, animals, and water to a certain extent. In many regions of the world, the plant is referred to by various local names. For instance: Heglig (tree), Lalob (fruit); trade names include Zaccone, Hingot, Bedeno, Egyptian balsam (Fadl, 2015; Goyanar *et al.,* 2020). Various traditional medical uses for *B. aegyptiaca* including antidiabetic, anti-feedant, molluscidal, anti-cough, and anthelmintic have been reported (Yassin *et al.,* 2017). There has already been an attempt to review the plant (Al-Thobaiti *et al.,* 2018). However, as per our literature search, no current comprehensive biological reviews of *Balanites aegyptiaca* is available. The present review provides an up-to-date and exhaustive analysis of the research done on the biological potential of *B. aegyptiaca*.

2. BRIEF TAXONOMIC DISTRIBUTION

An evergreen dicotyledonous multi-branched Savannah tree species, *Balanites aegyptiaca,* is endemic to dry and semi-arid regions of Africa, the Arabian Peninsula, and South Asia (Shalaby *et al.,* 2010; Vijay *et al.,* 2010; Gardette *et al.,* 2013). *B. aegyptiaca* is a fruit-bearing tree native to Africa that is found in tropical and subtropical climates, ranging from Senegal in west to Somalia in east, and from Jordan in north to Zimbabwe in south (Goyanar *et al.,* 2020). It is also available in Saudi Arabia, India, Iran, Jordan, Syria, Oman, Palestine, Myanmar and Yemen (Abdalla *et al.,* 2022). They are described as woody found in a diverse area of ecological settings and flourishes in arid climates (Vijay *et al.,* 2010; Kusch *et al.,* 2011; Khamis *et al.,* 2020). It grows at an altitude between 380 and 1,800 m masl and encounters rainfall amounting to 100-1400 mm (Khamis *et al.,* 2020). *B. aegyptiaca* developed a new adaptation approach to the harsh climate of these places. It appears a triple root system that accepts it to gain control any drop of moisture that is in contact with it (Gardette *et al.,* 2013); thus, helps to survive for at least two years without rain (Gardette *et al.,* 2013). *B. aegyptiaca*, also known as desert date tree, is a member of the family Zygophyllaceae (Khamis *et al.,* 2020). This tree reaches a height of 10 m and possesses a light crown with intense thorns. Various types of inflorescences, plus yellow-green, bisexual blooms that produce nectar, are generated by the tree (Kusch *et al.,* 2011).

3. TRADITIONAL THERAPEUTIC USES

People have traditionally recognized plants as one of the most valuable parts of the biosphere due to their nutritional and medicinal functions and chemical properties. All parts of plant *B. aegyptiaca* are used for medicinal reasons. The fruits of this plant are used to cure a variety of illnesses, including diarrhoea, dysentery, fever, syphilis, constipation, wound healing, and intestinal worm infestations (Doughari *et al.,* 2007). *B. aegyptiaca* roots and bark are known for their purgative and anthelmintic properties. Swelling and stomachache are also relieved by its root, while bark is used to deworm animals (Abdalla *et al.,* 2022). *B. aegyptiaca* fruit is used in Sudan and Egypt to treat jaundice (Habieballa *et al.,* 2021). A wide variety of ailments are treated by the oil extracted from the seeds, including epilepsy, syphilis, jaundice, and even jaundice. In traditional African medication, the bark is utilised for the treatment of skin diseases and wound healing (Sedky *et al.,* 2022). *B. aegyptiaca* parts are used for the management of diabetes and liver diseases (Shalaby *et al.,* 2010). The extract from its bark is used to eliminate copepods and freshwater snails (Sarker *et al.,* 2000; Maregesi *et al.,* 2008). The mesocarps fruits are additionally used to remedy water fleas, which assist as guinea worms' alternate hosts, and freshwater snails, which serve as bilharzia's intermediate hosts (Shalaby *et al.,* 2010). Numerous illnesses, including wounds, syphilis, hemorrhoids, jaundice, intestinal worm infection, malaria, dysentery, constipation, diarrhoea, stomachaches, asthma, and fever have historically been treated with it (Fig. 1) [Ibrahim, 2016]. Malaria is another disease treated by using *B. aegyptiaca* root (Habieballa *et al.,* 2021). Due to the presence of active ingredient steroidal saponin, the bark was once utilized as a fish poison (Neuwinger, 2004). Fruits are sold as an antidiabetic by herbalists in the Egyptian market (Deib *et al.,* 2018), and they are used orally as an anti-hyperglycemic

in Egyptian traditional medicine (Gad *et al.*, 2006; Zaahkouk *et al.*, 2015; Zaky *et al.*, 2022). Root decoction is typically used to treat malaria. The roots are used to alleviate edema and stomach troubles when heated into a soup, while the bark is used to deworm animals. As an oral hypoglycemic, its fruits are used in traditional Egyptian medicine (Ahmed *et al.*, 2015). Extracts from the plant roots, branches, bark, fruit, and kernel have proven to be toxic to the miracidia and cercariae of *Shistosoma mansoni* and *Fasciola gigantica*, both of which are gastrointestinal parasites (Koko *et al.*, 2000).

4. THERAPEUTIC BIOLOGICAL ACTIVITES OF *B. aegyptiaca*

4.1 Antioxidant activities

The primary factor behind the health benefits of plant-derived natural bioactive compounds is their ability to reduce oxidative stress (Laus *et al.*, 2023). Phytochemicals are a diverse group of secondary metabolites that plants produce and store. There are two main sources for these chemicals: constitutive production and stress-induced formation (Kasote *et al.*, 2015). Human body has an antioxidant defense system in place to counteract the oxidative stress brought on by the production of free radicals and reactive oxygen species (ROS) during typical physiological operations (Abdulrahman, 2023). Since antioxidants can shield the body from the harmful effects of free radicals and ROS, therefore, many chronic diseases can be prevented or even cured.

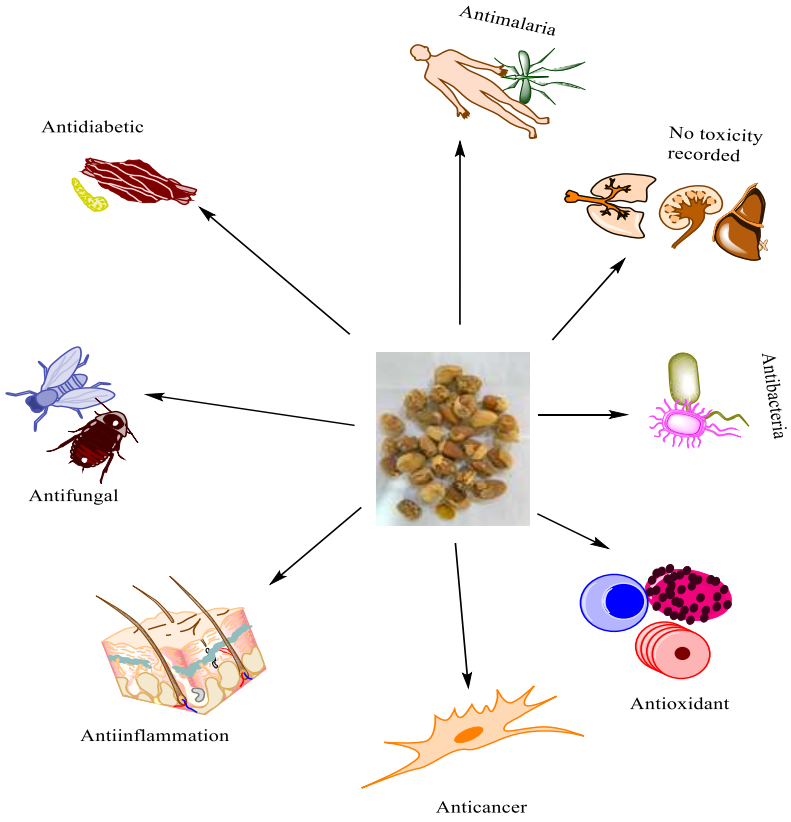

Fig. 1: Summary of biological activities of *Balanites aegyptiaca*

The perusal of literature has revealed the presence of high antioxidant content in *B. aegyptiaca* in its different parts (Table 1). The addition of *B. aegyptiaca* extract at a concentration of 20 µg mL^{-1} variably inhibited β-carotene bleaching (Abdallah *et al.*, 2012). *B. aegyptiaca* showed anti-oxidant activity in FRAP or DPPH assays (46.8 and 102.0 g AAE g^{-1}, respectively) [Nitiema *et al.*, 2020]. Low levels of radicals can be scavenged by hydro-ethanolic extract of *B. aegyptiaca* ($IC_{50.}$ 52.5 µg mL^{-1}). The ferric reduction in this sample is 126 moles (Anani *et al.*, 2015). The IC_{50} value for inhibiting free radicals in methanolic leaf extract was 182 µg mL^{-1} (Kahsay *et al.*, 2014). After pretreatment with leaf extract, these changes were prevented and the enzyme activities were restored to almost normal levels, which was statistically significant ($P < 0.05$) [Masry *et al.*, 2010]. The overall antioxidant capacity of ethanolic root extract ranged from 55 to 81%, whereas the concentrations of aqueous root extract ranged from 20 to 35% as compared to the 80% for regular ascorbic acids (Usman *et al.*, 2010). Chloroform fruit extract had highest level of radical scavenging activity (75%), while hexane and methanol extracts had scavenging capacities of 44 and 41%, respectively (Al-Ashaal, 2017). The different dosages of extracts significantly corrected the negative effect of *Monosodium glutamate* on memory (Parfait *et al.*, 2022). This was demonstrated

Table 1: Biological evaluation of *Balanites aegyptiaca*

S. No.	Biological activity	Method Followed	Plant part used	Solvents used	Concentrations tested	Reference
1	Antioxidant	DPPH	Fruits (oil)	n-hexane	1 mL	Al Ashaal *et al.* (2010)
		DPPH	Fruits	-	-	Abdelaziz *et al.* (2020)
		DPPH, β-carotene bleaching assay	Fruits	Methanol	200, 500 µL	Abdallah *et al.* (2012)
		DPPH, ABTS, FRAP	Stem bark	n-hexane, chloroform, methanol, aqueous	20, 100 µL	Hassan *et al.* (2016)
		DPPH, FRAP	Stem bark	Ethanol (70%)	-	Nitiema *et al.* (2020)
		DPPH, FRAP	Bark	Ethanol-aqueous (7:3)	50–100 mg mL^{-1}	Anani *et al.* (2015)
		DPPH	-	Methanol	-	Annan *et al.* (2008)
		DPPH, FRAP	Fruits	Aqueous	1.5- 5.0 mg mL^{-1}	Amadou *et al.* (2012)
		DPPH, FRAP	Leaves	Ethanol	-	Khamis *et al.* (2020)
		In vivo	-	Ethanol	100, 200 mg kg^{-1}	Suky *et al.* (2011)
		In vivo	Fruits	-	100 mg kg^{-1}	Montasser *et al.* (2017)
		In vivo	Leaves	-	400 mg kg^{-1} BW	El Masry *et al.* (2010)
		In vivo	Fruits	Ethanol	-	Jaheed *et al.* (2019)
		DPPH	Root	Ethanol, aqueous	100 mg mL^{-1}	Usman *et al.* (2010)
		DPPH	Fruits	-	-	Kabbashi (2015)
		DPPH	Fruits	-	1.5 mg mL^{-1}	Sedky *et al.* (2022)
		DPPH	Leaves	Methanol	-	Ibrahim (2016b)
		DPPH	Fruits	Hexane, chloroform, methanol	-	Al-Ashaal (2017)
		Thiocyanate method	Leaves	Ethanol	200-1000 µg	Vijay *et al.* (2010)
			Fruit pulp	Aqueous	50, 125, 250, & 500 mg kg^{-1}	Parfait *et al.* (2022)
		DPPH	Leaves	Methanol	1 mg mL^{-1}	Kahsay *et al.* (2014)
		DPPH, super-oxide radicals	Fruits	-	5 mg mL^{-1}	Amadou *et al.* (2017)
		DPPH	Kernel	Ethanol	50- 200 mg mL^{-1}	Mostafa *et al.* (2016)
		In vivo	Fruits	Methanol	-	El-Saied *et al.* (2021)
		DPPH	Seed	-	-	Badu *et al.* (2021)
		DPPH, FRAP	-	-	-	Nitiema *et al.* (2020)
2	Anti-inflammatory	*In vivo*	Bark	Methanol, butanol	200, 400 mg kg^{-1}	Speroni *et al.* (2005)
		In vivo	Oil	-	25-100 mg kg^{-1}	Ahmed *et al.* (2015)
		In vivo	-	Aqueous	-	Elkareem *et al.* (2021)
		-	Galls, leaves	Aqueous, acetone		Meda *et al.* (2020)
		Protein denatu-ration assay	Seed	-	-	Badu *et al.* (2021)
		In vivo	Seed oil	-	10-600 mg kg day^{-1}	Goyanar *et al.* (2020)
		In vivo	Bark	Methanol, butanol	-	Speroni *et al.* (2005)
3	Antibacterial	Disc	Leaves	Aqueous, acetone & ethanol.	20-100 mg mL^{-1}	Doughari *et al.* (2007)
		Agar-well diffusion	Fruits	Methanol	50, 100 mg mL^{-1}	Abdallah et al. (2012)
		=	Bark	-	Ethanol-aqueous (7:3)	Anani *et al.* (2015)
		-	Fruits	Ethanol	-	Kabbashi (2015)

		-	Stem bark, galls	Methanol	10 mg mL^{-1}	Ouedraogo *et al.* (2018)
		Disc diffusion	Leaves	Methanol	-	Kahsay *et al.* (2014)
		Well diffusion	Kernel	Ethanol	50-200 mg mL^{-1}	Mostafa *et al.* (2016)
		Agar diffusion	Fruits	Methanol	15.6-1000 µg mL^{-1}	Ibrahim *et al*. (2022)
		Agar plates	Leaves, stem bark, root bark	Aqueous (hot & cold) and ethanol	100 mg mL^{-1}	Tula *et al.* (2014)
		Agar well diffusion	Leaf	Aqueous, ethanolic	200, 100, 50, 25, 12.5, 6.25 mg mL^{-1}	Ezemokwe *et al.* (2020)
			Seed	n-hexane	100, 50, 25, 12 , 6 µg mL^{-1}	Habieballa *et al.* (2021)
		Disc	Leaves	Methanol, aqueous	5, 10, 15 mg mL^{-1}	Abdulhamid *et al.* (2016)
		Ager well	Leaf, stem, fruit and flower	Ethanol	-	Shahid *et al.* (2012)
		Disc	Galls, leaves	-	40 mg mL^{-1}	Meda *et al.* (2011)
		Agar well diffusion	Mesocarp	Aqueous	-	Awad *et al.* (2013)
		Disc	Leaves	Methanol, aqueous	5, 10, 15 mg mL^{-1}	Abdulhamid *et al.* (2016)
			Leaves		25-100%	Ibrahim (2016a)
4	Antifungal	Agar-well diffusion	Fruits	Methanol	50, 100 mg mL^{-1}	Abdallah *et al.* (2012)
		Disc	Fruits (oil)	n-hexane	10 µL per disk	Al Ashaal *et al.* (2010)
		Disc	Seed, callus		-	Abaka *et al.* (2020)
			Seed		100, 50, 25, 12, 6 µg mL^{-1}	Habieballa *et al.* (2021)
		MIC	Fruits		-	Khatoon *et al.* (2013) Nitiema *et al.* (2019)
5	Antiparasitic		Fruits	Hexane, chloroform, methanol	-	Al-Ashaal (2017)
		In vivo	Fruits	Methanol	1,000 mg kg^{-1} BW	Shalaby *et al.* (2010)
		In vivo	fruit mesocarp	Chloroform, ethyl acetate, butanol, methanol	0- 0.200 % w/v	Wiesman *et al.* (2006)
		In vivo	Fruit mesocarp	Aqueous	9 g kg^{-1} BW	Koko *et al.* (2000)
		In vivo	Fruit mesocarp	-	200 mg kg^{-1} BW	Koko *et al.* (2005)
		In vivo	Leaf, fruit pulp, seed kernel	Aqueous	0, 0.1, 0.2, 0.5, 1.0, & 2.0%	Chapagain *et a-l.* (2005)
		In vivo	Root (callus)	-	0, 50, 100, 500, 1000 &1500 ppm	Chapagain *et al.* (2008)
			Leaves, stem back, roots	Aqueous	10- 50 ppm	Abdullahi (2018)
		In vivo	Seed	Aqueous	1.25 g 100 mL^{-1}	Kusch *et al.* (2011)
		In vivo	-	-	-	Karou et al. (2011)
6	Antidiabetic	*In vivo*	Fruits	Aqueous	1.5 g kg^{-1} bw daily for 45 days	Erejuwa *et al.* (2012)

		In vivo	-	Butanol, dichloromethane	50 mg kg^{-1} bw	Hassanin *et al.* (2018)
		In vivo	Seeds	Aqueous	4.2 mg 100 g^{-1}	Helal *et al.* (2013)
		In vivo	Fruit, seed	Aqueous	200 mg kg^{-1} bw day^{-1}	Zaky *et al.* (2022)
		In vivo	Fruits	Aqueous	-	Deib *et al.* (2018)
		In vivo	Seeds	-	-	Gad *et al.* (2006)
		In vivo	Fruits	Ethyl acetate	10-50 mg kg^{-1} bw	Al-Malki *et al.* (2015)
		In vivo	Kernel	Methanol	650 mg kg^{-1}	Al-Thobaiti *et al.* (2019)
		In vivo	Fruits	Ethanol, butanol, dichloromethane	50 mg kg^{-1} day^{-1}	Al-Ashaal (2017)
		In vivo	Fruits	Aqueous	0.25-1.0%	Ghanem *et al.* (2016)
7	Wound healing	*In vivo*	-	Methanol	33.3% w/w	Annan *et al.* (2008)
8	Anti-Alzheimer	-	Pulp	-	-	Ibrahim *et al*. (2021)
9	Antiviral	-	Fruit(oil)	N hexane	-	Al Ashaal *et al*. (2010)
10	Anticancer	*In vivo*	Fruits	-	10 mg kg^{-1} bw	Al-Ghannam *et al.* (2013)
		MTT	Root	Methanol	1-10 µM	Beit *et al.* (2011)
		-	Fruits	Hexane, chloroform, methanol	-	Al-Ashaal (2017)
		In vivo	Fruits	-	400 mg kg^{-1}	Issa *et al.* (2015)
		MTT	Fruits	Methanol	31-1000 µg mL^{-1}	Ibrahim *et al.* (2022)
		-	Fruits	-	-	Yassin *et al.* (2017)
		Sulphodiamine-B (SRB) assay	-	Methanol	-	Zaahkouk *et al.* (2015)
		MTT	Seeds	-	3.12-100 µg mL^{-1}	Sherif *et al.* (2016)
		MTT	Fruits	Ethyl acetate, ethanol, chloroform	25-100 µg mL^{-1}	Al-Malki *et al.* (2016)
		ELISA	Fruit oil	n-hexane	-	Al Ashaal *et al*. (2010)
11	Toxicity	Micronucleus & chromosomal aberrations assays	Fruit oil	n-hexane	50 & 100 ppm	Al Ashaal *et al.* (2010)
		MTT	Leaves	Methanol	125- 500 µg mL^{-1}	Ibrahim (2016b)
		In vivo	-	Aqueous	1 g kg^{-1}	Ali *et al.* (2001)
		In vivo	Fruits	-	8.4-64 g L^{-1}	Absalom *et al.* (2013)

by a significant ($P<0.05$) increase in the proportion of spontaneous alternation in Y-maze test and a significant ($P<0.05$) increase in the discrimination index for recognizing novel items at a dose of 500 mg kg^{-1} extract (Parfait *et al.*, 2022).

Methanol extract showed highest level of free radical activity in DPPH experiment ($IC_{50,}$ 40 µg mL^{-1}), and the highest level of antioxidant activity in FRAP 0.52 ($FeSO_4$ mol mL^{-1}) assay (IC_{50}, 125.85 µg mL^{-1}) {Hassan *et al.*, 2016]. The antioxidant activity of *B. aegyptiaca* oil is greater than that of normal oleic acid due to the synergistic impact of oleic, linoleic, and sterol acids (Al Ashaal *et al.*, 2010). Serum levels of GOT, GPT, and ALP were significantly higher in the CCl_4 intoxicated group (group II) as compared to the healthy control group ($P<0.01$). (group I). Compared to the control group, CCl_4-intoxicated rats had considerably lower total protein (4.31 g dL^{-1}) and albumin (2.61 g dL^{-1}), both of which were statistically significant ($P<0.01$) (Suky *et al.*, 2011). TNF-levels oxidized glutathione (GSSG), malondialdehyde (MDA), and nitric oxide were also significantly elevated in MTX 40, as were alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total and direct bilirubin, and oxidized glut. Nonetheless, the MTX-treated group showed markedly lower levels of total protein, albumin, total antioxidant capacity, reduced glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR),

glutathione S-transferase (GST), superoxide dismutase (SOD), and catalase (CAT) (Montasser *et al*., 2017). Due to an increase in flavonoids, which have high free radical scavenger properties and significant antioxidant activity, this happened linearly with increasing doses (Mostafa *et al.,* 2016). The extract, which contains saponins, flavonoids, terpenoids, phenolics, and alkaloids showed *in vitro* antioxidant activity (Jaheed *et al.,* 2019). An important predictor of a compound's potential antioxidant action is its capacity for lowering (Vijay *et al.,* 2010).

The ability of medicinal plants to effect therapy is typically linked to the variety of secondary metabolites they contain (Yılmaz *et al.,* 2023). Due to their many useful biological and pharmacological features, including their potent antioxidant effects, phenolic acids are often regarded as a potential class of plant secondary metabolites. However, several processes, including the inhibition of chain initiation, binding of the transition metal ion catalyst, breakdown of peroxides, inhibition of abstraction, and radical scavenging, have been proposed to explain the antioxidant actions of putative antioxidants (Vijay *et al.,* 2010).

4.2 Anti-inflammatory activities

There has been recent surge in the use of therapeutic plants as scientific research now backs up their usage in folk medicine to treat common disorders like inflammation, fever, cold and cough (Dogara, 2023). Injured or infected tissues trigger a defensive reaction known as inflammation (Abdulrahman, 2023). This is normal during recovery process but can be a problem in and of itself. Inflammation is characterized by redness, swelling, pain, heat, and dysfunction (Dogara, 2023). The inflammatory processes underlying these symptoms are triggered and regulated by a plethora of chemical mediators present in plants (Abdulrahman, 2023). These include complement proteins, kinins, eicosanoids, monokines, and histamines. For millennia, the leaves, root, bark, fruit, and seeds of *B. aegyptiaca* have been used as a medicine to alleviate inflammation and its associated symptoms (Deib *et al.,* 2018).

The crude extract of *B. aegyptiaca* prepared in a variety of solvents has been found efficient in treating a variety of inflammatory diseases. The extract induced significant inhibition of 63.9% when used @ 600 mg kg^{-1} (Goyanar *et al*., 2020). The aqueous extract significantly reduced serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, urea, creatinine, tumour necrosis factor alpha, and interleukin-1beta levels, as well as hepatic malondialdehyde and nitric oxide (NO) levels (Elkareem *et al*., 2021). The aqueous and acetone extracts significantly ($P<0.0001$) decreased the levels of total leukocytes, total nitrite, and total nitrate in rat's serum (Meda *et al.,* 2020). Oil reduced edema-induced increases in NO, LPO, CAT, and GST enzyme activity. Both methanol and butanol extracts exhibited strong analgesic effectiveness at 400 mg kg^{-1}. The number of writhes in mice treated with bark extract is significantly reduced. Mice pretreated with saponins, or extracts @ 200 mg kg^{-1} did not vary from the control group (Speroni *et al.,* 2005). The effects of butanol extract are clearly dose-dependent and are more pronounced than those of methanol extract (Speroni *et al*., 2005). Edema was reduced because of lower levels of cyclooxygenase-2 (COX-2), tumour necrosis factor-alpha (TNF-a), and interleukin-6 (Ahmed *et al*., 2015). Butanol extract demonstrated promising dose-response activity, with volume inhibition in rat paw ranging from 59 to 62.5% at a dose of 200 mg kg^{-1} (Speroni *et al*., 2005). The structures of two saponins (steroid saponins 1 and 2) may explain the anti-inflammatory activity generated by the administration of *B. aegyptiaca* extracts (Speroni *et al.,* 2005). Many anti-inflammatory herbal medications have various forms of saponins as major ingredients. Saponins may generate a modification of antioxidant systems that justify the pharmacological activity (Sayyah *et al*., 2004). The data provides significant support to the hypothesis that certain chemicals found in *B. aegyptiaca* extracts may inhibit lipoxygenase and/or cyclo-oxygenase (Speroni *et al.,* 2005). The local peritoneal receptors presumably play a role in abdominal writhing response. Prostanoid system involvement appears crucial for the mechanism of response to this nociceptive stimulation. Multiple studies have found elevated levels of peritoneal fluid prostaglandin E_2-induced inflammation (PGE_2 and PGF_2), as well as lipoxygenase products (Dhara *et al.,* 2000). The receptors of tyrosine kinase are influenced by a number of stress and pathologies which, in turn, promote IKKs. The energetic IKKs phosphorylate dormant IκBα-NF-κB complex. The IκBα,

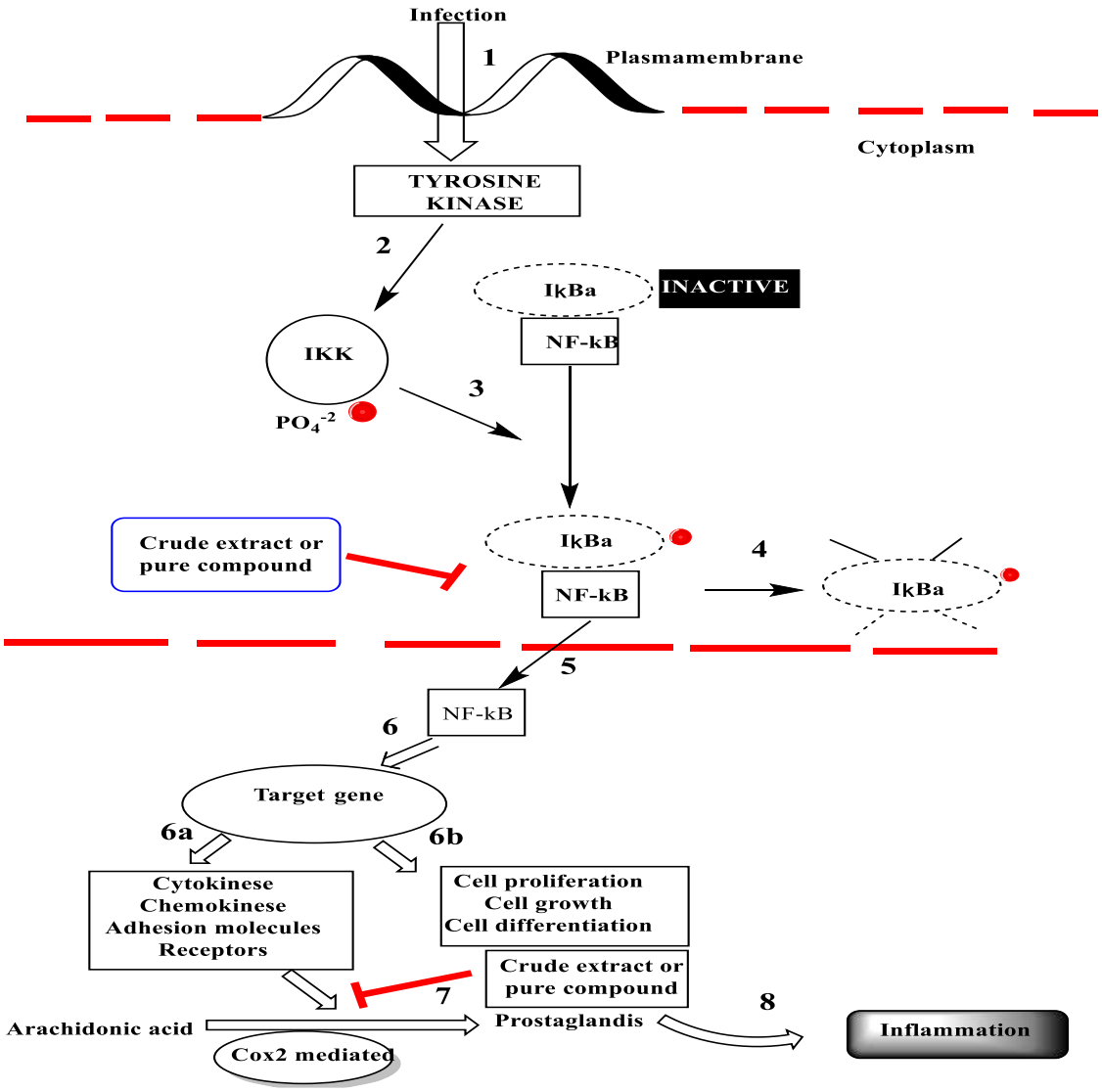

Fig. 2: Illustration of the anti-inflammatory mechanism of action of *B. aegyptiaca*

when phosphorylated go through ubiquitylation, and is later degraded. The pure compound or crude extract prevent the access of active form of NF-κB into nucleus which helps the expression of genes intricate in (6a), chemokines, adhesion molecules, cytokines and adhesion molecules altogether partake a protagonist in (6b) differentiation, growth and cells proliferation. With the help of Cox2, arachidonic acid exchanged into prostaglandin, nevertheless a pure compound or crude extract will stop this from happening. This inflammation is triggered by prostaglandins (Fig. 2). The present review's innovative and supportive findings recommend further exploration into the plant's anti-inflammatory properties.

4.3 Antibacterial activities

Due to the alarming global proliferation of multidrug resistance bacteria, the development of novel antimicrobial medicines derived from plants is of utmost importance. Owing to the rise in antibiotic-resistant pathogens, it is critical to develop new antibacterial medicines with unique targets. The methanol extract demonstrated significantly higher antibacterial activity *in vitro* than the standard antibiotic (gentamicin 1 mg mL^{-1}) [Abdallah *et al.*, 2012]. At a dosage of 100 mg mL^{-1}, *Bacillus cereus* showed the greatest susceptibility (22.3 mm), followed by *B. subtilis* (22.2 mm). Inhibition zones of

all strains tested were > 14 mm, indicating that the extract has great potential as an efficient antibacterial agent against a wide variety of bacterial pathogens (Abdallah *et al.,* 2012). Further, the organic extracts (acetone and ethanol) were more active than the aqueous extracts. The extraction capabilities and solubility profiles of phytoconstituents reportedly vary significantly between the solvents (Doughari *et al.,* 2007). Moreover, the effectiveness of plant extracts was comparable to that of antibiotics ciprofloxacin, cotrimoxazole, and chloramphenicol. When used at 100 mg mL^{-1} (16 mm zone of inhibition), ethanolic extracts of *B. aegyptiaca* outperformed the other antibiotics and ciprofloxacin (10 mg mL^{-1}, 10 mm zone of inhibition) in killing bacteria. This showed that the plant extracts work well as anti-typhoid agents if used in purified form (Doughari *et al.,* 2007).

At the concentrations of 400 and 800 mg mL^{-1}, the extract exhibited substantial antibacterial activity against Gram-positive and Gram-negative bacteria isolated from clinical and subclinical mastitic cow (Murthy *et al.,* 2020). At higher concentrations, the extract's antimicrobial effectiveness was more pronounced (Murthy *et al.,* 2020). Methanol extract of *B. aegyptiaca* fruit showed significant levels of total phenolics and total flavonoids, as well as the presence of saponins and terpenoids, phenolic compounds, and alkaloids (Abdallah *et al.,* 2012). Phenolics, terpenoids, alkaloids, lectins, polypeptides, and poly-acetylenes were identified as the most common types of antimicrobial chemicals found in plants (Abdallah, 2011). Antimicrobial substances such as phenolics (simple phenols, quinones, phenolic acids, flavonols, flavones, flavonoids, tannins, coumarins, terpenoids, essential oils, and alkaloids) are prevalent in desert date (Murthy *et al.,* 2020). Possible antibacterial properties of this plant are due to the presence of saponins and alkaloids (Doughari *et al.,* 2007). The penetration of extract into the cell harm intracellular organelles (Gonelimali *et al.,* 2018). The extract's induction of cellular toxicity and oxidative stress caused by the production of ROS and free radicals, and the extract's modulation of cellular signalling are the four well-defined mechanisms linked to the antimicrobial action of plant extract.

4.4 Antifungal activities

Fungi can induce opportunistic infections in patients having weakened immune systems as a result of an underlying illness or the use of immunosuppressive medications (Khatoon *et al.,* 2013). Even though many antifungal medicines have been developed, only a few are clinically efficacious and safe to use (Khatoon *et al.,* 2013). This predicament has compelled researchers to seek new antibacterial substances from a variety of sources, including medicinal plants (Abdulrahman, 2022; Dogara, 2022; Dogara *et al.,* 2022). Plant-based antimicrobials have proven successful in treating numerous infectious diseases vis-à-vis minimizing many negative effects commonly associated with synthetic antimicrobials (Samy *et al.,* 2000). The plant extract used @ 100 mg mL^{-1} demonstrated antifungal activity against all the test fungal strains, with inhibition zones greater than observed in reference antibiotic (amphotericin B, @ 2 mg mL^{-1}); with highest susceptibility in *Aspergillus niger* (24.8 mm), followed by *Fusarium graminearum* (20 mm) (Abdallah *et al.,* 2012). When applied @ 10 µL per disk, the oil killed all microbiological strains tested. Maximum inhibitory concentrations for *Candida albicans* were reported to be 22 and 20 mm for *Staphylococcus aureus* (Al Ashaal *et al.,* 2010). The methanolic extract of callus had largest zone of inhibition, measuring 17 and 11 mm, respectively, at doses of 100 and 50 mg mL^{-1}, respectively (Abaka *et al.,* 2020). An inhibitory zone of 21 mm was observed for *Candida albicans* at the dose of 100 µg mL^{-1} (Habieballa *et al.,* 2021). Against the tested fungi, the minimum inhibitory concentration (MIC) for an alcoholic fruit extract was 3.05-24 µg mL^{-1}, whereas the MIC for an *in vitro* produced callus extract was 1.53-12 µg mL^{-1} (Khatoon *et al.,* 2013). The extract prevented the growth of all fungus's mycelium, and this action was concentration dependent. *Fusarium solani* and *F. moniliforme* required a 1% extract concentration while *Curvularia lunata* needed a concentration of 0.5% to entirely stop mycelial growth. (Nitiema *et al.,* 2019).

4.5 Anti-parasitic activities

The parasites that have adapted to humans as hosts have proliferated throughout our history. Most parasites are annoying or harmful to human health (Wink, 2012). Malaria, trypanosomiasis, and

Chagas disease are all parasite illnesses that can be fatal if not treated promptly and effectively (Wink, 2012). The two most pervasive parasite illnesses that impact people are leishmaniasis and malaria (Tariq *et al.*, 2016). Medications that are effective against several endoparasites have been developed in the field of medicinal chemistry. Although many of these drugs were developed many years ago, some parasite strains have developed resistance to them. Due to mounting evidence of existing anthelmintic drug resistance and declining potency against parasites in their encapsulated larval stages, there is a great interest in creating novel anthelmintic medications, particularly those derived from medicinal plants (Shalaby *et al.*, 2010). The parasite was totally destroyed on exposure to crude plant extract after 3 days, with a determined IC_{50} value of 68 µg L^{-1} (Kusch *et al.*, 2011). On 3rd and 5th day, the extracts of methanol and chloroform demonstrated 100% elimination of Schistosoma worms. Both the extracts demonstrated anti-fascioliasis action as evidenced by their LC_{50} values of 63 and 55 mg L^{-1} (Al-Ashaal, 2017). At a concentration of 0.0014% (w/v) of this active component, 50% larval population was inhibited from emerging as adults (Wiesman *et al.*, 2006). As per percentage reduction in fluke counts in liver post-mortem two weeks after medication, the extract was 97.7% effective. In terms of egg g^{-1} faeces, packed cell volume (PCV), haemoglobin concentration, total red blood cell count (RBC), total white blood cell count (WBC), and eosinophil, liver fascioliasis lesions were significantly different between control and treatment groups ($P< 0.05$) (Koko *et al.*, 2000). The fruit extract significantly decreased EPG (eggs g^{-1} stool), egg burden in tissues, and adult worm recovery ($P <0.05$) (Koko *et al.*, 2005). The 0.5% aqueous bark extract caused death of all larvae (Chapagain *et al.*, 2005). In a chronic mortality examination, 500 ppm or more could entirely eradicate the test larvae population (after 7 days of exposure) (Chapagain *et al.*, 2008). The extract had a modest anti-plasmodial effectiveness, with an IC_{50} of 24.56 µg mL^{-1} (Karou *et al.*, 2011). The current research details the effectiveness and dependability of *B. aegyptiaca* in treating a wide range of parasites, and it also calls for scientists' attention to other scientifically validated species that might result in the development of innovative antiparasites medications.

4.6 Antidiabetic activities

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia caused by defects in insulin secretion, action, or both (Deib *et al.*, 2018). About 422 million people throughout the world currently suffer from diabetes, and this number is significantly on rise. As per the conservative estimates of WHO, this figure is likely to double during next two decades (Ghanem *et al.*, 2016). The International Diabetes Federation (IDF) has revealed that 463 million adults (aged 20-79 years) worldwide have diabetes; most of these people reside in low-income and developing regions (Zaky *et al.*, 2022). This number is anticipated to rise to 700 million by 2045. Population expansion, urbanization, nutritional transition, physical inactivity, and dietary change all contribute to the rise in DM (Zaky *et al.*, 2022). The current synthetic antidiabetic medications have a number of advantages, but also have undesirable side effects (Osadebe *et al.*, 2014). Hence, new antidiabetic drugs that produce fewer or no harmful side effects are required. Lately, active medications with antidiabetic activity have been derived from plants, and they are more effective than oral chemical hypoglycemic pharmaceuticals now used in established therapy (Verma *et al.*, 2018). Many bioactive chemicals found in medicinal plants stimulate insulin secretion as well as insulin activity (Zaky *et al.*, 2022). As a result, *in vitro* and *in vivo* data were pooled to determine the total impact of *B. aegyptiaca* on diabetes. There was a striking difference between the treated and untreated groups, with treated groups showing significantly greater pancreatic weight, larger islets of Langerhans, and enhanced histoarchitecture (Abou Khalil *et al.*, 2016). As an alternative treatment for DM, medicinal plants are widely used in underdeveloped countries due to their demonstrated efficacy in lowering plasma glucose levels with little adverse effects. Research on natural antidiabetic therapies, such as medicinal plants, that have little or no adverse effects is in high demand (Erejuwa *et al.*, 2012). The administration of aqueous extract of fruits significantly boost serum insulin in diabetic rats (91%), while lowering blood sugar levels (54%), cholesterol levels (26%), triglyceride levels (16%), and LDL cholesterol levels (25%) (Deib *et al.*, 2018). The damaging effects on serum insulin and C-peptide levels, oral

glucose tolerance, liver lipid peroxidation, liver glucose-6-phosphatase and glycogen phosphorylase activities, serum lipid profile, serum free fatty acid level, glutathione content, and antioxidant enzyme (glutathione peroxidase, glutathione reductase, and glutathione S-transfer) levels were significantly reduced in diabetic-treated rats with extract (Zaky *et al.*, 2022). The seed extract significantly lowered hepatic glucose-6-phosphatase activity and blood glucose levels in diabetic rats, lowering both by 24% (Gad *et al.*, 2006). Hexane, chloroform, and methanol fruits extracts all reduced blood sugar levels by 64, 69, and 77%, respectively (Al-Ashaal, 2017). After four weeks of fruit therapy, diabetic rats had significantly lower levels of blood sugar, urea, creatinine, AST, ALT, total cholesterol, and triglycerides. The levels of total protein and the activity of several antioxidant enzymes were also higher in diabetes group than in control group, and the total antioxidant capacity was restored to almost normal levels (Ghanem *et al.*, 2016). Fruit ethyl acetate extract had a hypoglycemic impact, as evidenced by diabetic rats' fasting blood glucose and glycated hemoglobin levels being lower than they were in the control group (Al-Malki *et al.*, 2015).

The plant extract-treated diabetic rats displayed improvement in insulin, decreased glutathione level, catalase, and superoxide dismutase activities, as well as decrease in plasma glucose, HbA1c, lactic acid, lipid profile, and malondialdehyde as compared to the untreated rats (Hassanin *et al.*, 2018). After treatment with extract, the bulk of alloxan's toxic effects were diminished, and the histological changes caused by alloxan were partially reversed (Helal *et al.*, 2013). The extracts increased the serum levels of antioxidant enzymes CAT and SOD, as well as ALT, AST, ALP, and GGT. The extracts also shielded liver tissues from degenerative changes brought on by STZ (Al-Thobaiti *et al.*, 2019). Antioxidants compounds like vanillic acid, syringic acid and β-sitosterol were detected in GC-MS analysis of an ethyl acetate extract of fruits (Al-Malki *et al.*, 2015), which are likely responsible for antidiabetic activity of fruits. Saponins and a polysaccharide fraction in *Balanites* fruits are responsible for hypoglycemic impact (Gad *et al.*, 2006). Possible mechanisms for the extracts' anti-hyperglycemic and anti-hyperlipidemic actions in diabetic rats include elevating serum insulin levels, lowering insulin resistance, and bolstering the body's natural antioxidant defenses (Zaky *et al.*, 2022). Similarly, it was hypothesized that *B. aegyptiaca*'s mode of action results in a reduction in intestinal glucose absorption by suppressing amylase activity, which is regarded as the first line medication in the treatment of diabetes (Gad *et al.*, 2006; Deib *et al.*, 2018). Because of their effects on pancreatic beta cell activity, augmentation of inhibitory effect on insulinase enzyme, improvement of insulin sensitivity, and improvement of insulin-like activity, plant extracts are hypoglycemic. *B. aegyptiaca* fruit extracts have shown promising antidiabetic activities. As a result, the review opens new avenues for the development of antidiabetic drugs.

4.7 Other diseases treated with *Balanites aegyptiaca*

At a concentration of 50 µg mL^{-1}, the oil was more effective than acyclovir (60%) at killing Herpes simplex virus type 1(Al Ashaal *et al.*, 2010). After plant extract administration, the epithelization period was shortened from 26.7 (control) to 16.4 days, and the scar area was reduced while the tensile strength and hydroxyproline content were both considerably raised as compared to the control (Annan *et al.*, 2008). Extract efficiently inhibited acetylcholine esterase (IC_{50}: 193 µg mL^{-1}), butyrylcholine esterase (IC_{50}: 490 µg mL^{-1}), and tyrosinase (IC_{50}: 1.97 µg mL^{-1}) at incubation times of 10, 20, and 40 min, respectively (Ibrahim *et al.*, 2021). Further research is needed to determine the efficacy of *B. aegyptiaca* on viral illnesses, wound healing, and Alzheimer's disease.

4.8 Anticancer activities

Cancer is a multifactorial cell disease distinguished by aberrant cellular growth (Mbaveng *et al.*, 2011) and is a worldwide public health problem (Sherif *et al.*, 2016). Chemotherapy, radiotherapy, immunotherapy, and surgery are all part of cancer treatment routine in advanced grades and stages. However, net therapeutic outcomes are still associated with the significant side effects or unfavourable consequences (Al-Malki *et al.*, 2016). Medicinal plants have been at forefront of anticancer therapies (Abdulrahman, 2023). A wide range of plants and their separated compounds have anticancer action

(Abdulrahman, 2023). Modern research on cancer treatment is focused on maximizing the effectiveness while minimizing the adverse effects. Plant-derived chemicals have received increasing attention lately because of their anticancer properties and capacity to strengthen the body's defense. HepG2 and CaCo2 proliferation were influenced by *B. aegyptiaca* extract at nontoxic doses of 0.63 mg mL^{-1} of 81 and 77%, respectively (Yassin *et al.*, 2017). Zaahkouk *et al.* (2015) found that each extract had an inhibitory concentration (IC_{50}) of 2.3 for MCF7 cells, 12 for HEPG-2, and 69.3 for HCT116 µg mL^{-1}, respectively.

The significant antiangiogenic and antiproliferative effects of methanol extract may be due to its strong antioxidant component composition (Hassan *et al.*, 2016). Lymphoblastic leukemia, brain, liver, lung, and breast cell lines were all significantly affected by fruit extracts when tested against human cancer cell lines (Al-Ashaal, 2017). The oil's anticancer action was shown by the inhibition of the growth of human brain (U251) (IC_{50} 2.34 µg mL^{-1}), liver (HEPG2) (5.99 µg mL^{-1}), lung (H460) (4.77 µg mL^{-1}), and liver (HEPG2) carcinoma cell lines (Al Ashaal *et al.*, 2010). When the fruit extract was tested against MCF-7, PC-3, and Caco-2 cancer cell lines, it demonstrated considerable cytotoxic activity against each of them, with a selectivity index ranging from 5.07 to 6.52 (Ibrahim *et al.*, 2022). Increased total apoptosis of treated PC-3 cells (19.22% of the total number of cells) in comparison to control cells (0.64% of the total number of cells) and increased transcription of proapoptotic genes including P53 (3.69) and BAX (3.33) expressed as fold changes further corroborated this impact (Ibrahim *et al*., 2022). Balanitoside treatment reduced the number of EAC cells in both the treatment and preventive groups (Al-Ghannam *et al.*, 2013). MDA and NO levels in liver and serum were lower in therapeutic and preventive groups than in positive control group. Nevertheless, CAT activity was higher in therapeutic and preventive groups' liver and plasma than in positive control group (Al-Ghannam *et al.*, 2013). Caspase 3 activity was higher in treatment and prevention groups than in positive control group in EAC cells. Surviving expression in liver was lower in the therapeutic and preventive groups as compared to the positive control group (Al-Ghannam *et al.*, 2013). 3-O-d-xylo pyranosyl-(1–3) (1–3)-β-d-glucopyranosyl-(1–4)-[α-l-rhamnopyranosyl-(1–2)]-d-glucopyranoside), with IC_{50} values of 2.4 and 3.3 M, respectively, was reported to exhibit substantial antiproliferative effect against MCF-7 human breast cancer cells and HT-29 human colon cancer cells (Beit-Yannai *et al.*, 2011). With the administration of *B. aegyptiaca* extracts in ascetic fluid, a significant decrease in tumor volume, total cell volume, and viable cell count was seen. Further, it increased P53 expression, decreased lipid peroxidation, elevated SOD and CAT, and increased SOD (Issa *et al.*, 2015).

The A549 non-small cell lung cancer (NSCLC) (IC_{50}, 0.3 M) and U373 glioblastoma (IC_{50}, 0.5 M) cell lines were the most responsive to balanitin-6 and -7 (Gnoula *et al.*, 2008). The viability of seed extract against hepatic cancer (Hep-G2) cell line increased by 97.43% at 12.5 µg and reduced to 34.89% at 100 µg (Sherif *et al.*, 2016). When seed extract was applied to PC-3 cell line at a concentration of 3.125 µg, the activity peaked to 98.47% and then dropped to 26.74% (Sherif *et al.*, 2016). The ethyl acetate fruit extract had potent antiproliferative, apoptotic, and cell cycle phase modification effect when compared to vincristine (Al-Malki *et al.*, 2016). Numerous plant defense mechanisms have been linked to saponins (Francis *et al.*, 2002). Diosgenyl saponins (balanitin-6 and balanitin-7) isolated from *B. aegyptiaca* kernels have shown promising antitumor activity (Gnoula *et al.*, 2008). The primary cause of anticancer action is ATP depletion which, in turn, causes a significant disruption in actin cytoskeleton (Gnoula *et al.*, 2008). Another possible mechanisim is that the plant extract flow into the cells by endocytosis mediated through receptors. Cancer cell's pH level is acedic with a redox imbalance (Abdulrahman, 2023). Production of free radical increased as a result of extract (Abdulrahman, 2023), which resulted in damaging the membrane mitochondria, subsequently resulting in seeping out of protein material leading to the endoplasmic reticulum stress. The damage to mitochindrial membrane cause seeping out of numerous proteins and activation of caspases resulting in apoptosis. Several molecules pathways are activated. For example NF-κB, Wnt/β-catenin, MAPK/Erk, PI3K/Akt/mTOR, and apoptotic pathways are regulated by this state of cellular stress. The NF-κB upsets cellular homeostasis via inflammatory stress signaling pathway. Equally, carcinogenic signaling obliges the involvement of MAPK/Erk, VEGF, PI3K/Akt/ mTOR, and Wnt/β-

catenin pathways (Abdulrahman, 2023). More definitive evidence regarding the benefits of *B. aegyptiaca* fruits is needed, hence well-designed clinical trials are encouraged.

Medicinal herbs are used all around the world, especially in developing countries. This is because they are inexpensive and readily available locally. Because herbal treatments are natural, consumers all over the world believe they are always safe. But evidences reveal otherwise. These can be quite dangerous if not properly selected and prepared. Hence, it is vital to determine the safety of plant extracts. The maximal dosage of 500 µg mL^{-1} was shown to be safe (Ibrahim, 2016). The relationship between fish mortality and the concentrations used was positive ($r = 0.9811$). Prior to the fish's demise, some of the behavioural traits that were observed included erratic swimming on water surface, lack of reflexes, and hyperventilation. Hemoglobin estimation and packed cell volume (PCV) values were significant ($P < 0.05$) for acute lethal toxic dose (Absalom *et al.*, 2013). There has been less studies on the toxicity of species, thus research needs to focus on identifying the safest dosage for future studies.

5. CONCLUSION and FUTURE STRATEGIES

Balanites aegyptiaca is a multifunctional tree species valued for its medicinal properties as well as for its utility in providing food, clothes, animal feed, and raw materials for other utilitarian things. The entire plant is used for medicinal putposes across the Africa and various regions worldwide, owing to its intriguing pharmacological characteristics. *B. aegyptiaca* acts as a significant and plentiful source of vital nutrients. Both *in vitro* and *in vivo* studies have demonstrated that *B. aegyptiaca* has beneficial role in the prevention and treatment of numerous diseases. The tree has enormous potential as an antioxidant, antibacterial agent, and as protectant against diabetes and liver damage. It could potentially serve as a novel approach for treating the disorders. 1) It is crucial to comprehend the function and mechanism of action of each bioactive compound, as well as the potential therapeutic benefits that contribute to the creation of novel drugs. 2) There has been a lack of comprehensive investigations into the molecular mechanisms of action in pharmacological research. Instead, the majority of research has been carried out using *in vitro* and *in vivo* animal screening approaches. 3) Proteomic study on *B. aegyptiaca* provide a wealth of information on protein expression, function, interaction, networking, and biosynthetic pathways. 4) The data generated may be helpful in understanding the mechanism of illness prevention and designing new treatments. 5) Another area of research involves the preservation of *B. aegyptiaca* genotype for large-scale development of this plant, using seedlings that are propagated *in vitro*.

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