A review on Abelmoschus esculentus: A novel approach in the treatment of melasma

Aditi Gupta[1], Jitendra Singh Yadav[1], Arti Gupta*[1]

Shri Ram Murti Smarak college of Engineering and Technology (Pharmacy), Bareilly, Uttar Pradesh (243202)

***Corresponding Author:**

Dr. Arti Gupta

Director of pharmacy, Shri Ram Murti Smarak college of Engineering and Technology (Pharmacy), Bareilly, Uttar Pradesh 243202, India.

Emails: aarticognosy@gmail.com,

Mob no: +91- 9558848242

Abstract

Background-Melasma is a chronic dermatological problem marked by hyperpigmentation, it is caused because of the increment in melanin production which is directly influenced by UV rays, hormonal fluctuations, genetic predisposition or can be drug induced.

Main body-In this article we had considered all the available synthetic and natural treatments of melasma, their MOA, analysis of the phytomedicinal constituents used in treatment of melasma. Okra which is also known as abelmoschus esculentus is the main focused area of our review because of its novel anti-melanogenic properties in the treatment and management of melasma. We had discussed each and every single part analysis of okra followed by its extraction, evaluations and enlistment of its available formulations. Okra's cost-effectiveness, excellent antityrosinase and antioxidant properties makes it a potential alternative in the therapeutic management of melasma as melasma treatment is challenging, costly and marked with high reoccurrence. This hyperpigmentation causes significant impacts on the quality of life because no single treatment is universally efficacious and is marked with high side effects and high cost. According to our research okra can become the potential alternative of the available treatments of melasma because of its no side effects, easy availability, low cost, high stability, less maintenance, high compatibility with all skin types which makes it an effective and affordable treatment alternative. It either can be used as a single treatment or in combination with other drugs like hydroquinone and its derivatives. **Conclusion**-Okra's excellent antioxidant, anti-tyrosinase properties ,high concentrations of flavanols and catechins ,cost effectiveness makes it an effective and natural measure in the treatment and management of melasma over other treatments which are costly, unstable and can cause severe side effects over the long span of treatment.

Keywords-Melasma, Herbs, Phytoconstituents, okra, Okra formulations

Introduction

Melasma also known as hypermelanosis is a chronic dermatological condition/refractory disorder marked by hyper pigmentation (blemishes) due to increased melanin production in skin (1). It occurs dominantly in specific regions of face like Mandibular, Malar and Centrofacial regions of face (2)(3). Melasma is derived from the word “Melanin”, a pigment responsible for pigmentation in humans produced by the process of melanogenesis (4). Melanin (Photoprotective factor) is produced in “melanosomes’’ by “melanocytes” (Present on the side of basal epidermal layer), because of the stimulation of “keratinocyte cells” either by UV radiation or by Hormonal imbalance (like in pregnancy). Rather than just affecting looks of an individual it also has serious implications on mental health of the patient (5)(6).

Epidemiology

Prevalence rate of melasma among population lies between 8.8%-40%, where female to male ratio of melasma is 9:1or 34% in females and 6% in males. Occurrence rate of melasma among pregnant females is 50.8% which eventually gets disappeared almost within a year with relapse rate of 6% (7).Extent of melasma is higher among the population of the regions like India, Pakistan, china, Japan, middle-eastern and mediterrian countries where among the different skin types, type I and VI show the pigmentation of stable phenotype as type I skin shows controlled pigmentation whereas type VI shows the pigmentation at their maximum efficiency as per the data of the cases among European and negroid populations (8).

Clinical expressions of melasma

Bilateral, asymptomatic, light-to-dark brown macules or patches with uneven borders are the typical appearance of melasma (9)(10).

Centrofacial: top lip, forehead, cheeks, nose; majorly affected site, Malar — nose, cheeks, Mandibular: chin, jawline, Extrafacial: sun-exposed distribution
of the forearms, upper arms, and shoulders (11)(12)
The three forms of melasma are epidermal, dermal, and mixed—which are distinguished by the degree of elevated melanin in the skin (13)(14).

Etiology of melasma

Sun exposure: UV and visible light stimulate the formation of melanin.
One-quarter of the affected women with melasma have hormones fluctuations like in pregnancy whereas the use of oral contraceptives containing oestrogen or progesterone, intrauterine devices, implants, and hormone replacement treatment can also cause melasma.
Thyroid issues and melasma may be related (15)(16)(17). Medication and scented items: perfumed toiletries, cosmetics, and soaps may create a phototoxic reaction that results in melasma. These products are also innovative targeted therapy for cancer. The functions of neuronal, vascular, stem cell, and local hormonal variables in enhancing melanocyte activation are being investigated by researchers (18)(19)

Diagnosis

A skin biopsy may be taken on occasion. The histology of melasmas varies depending on the kind, but the following characteristics are usually present: In basal and suprabasal keratinocytes, melanin is deposited (20). Strongly pigmented marked by highly dendritic (branched) melanocytes within the dermal melanophages, melanin Solar elastosis and disintegration of elastic fibers marked by an expansion of blood vessels. (21)

Treatments

Treatments of melasma are classified into four categories of-

- Topical treatments
- Oral treatments
- Laser treatments
- Miscellaneous treatments

Topical treatments

Hydroquinone cream + Sunscreen 30 SPF, Sunscreen 30 SPF (Sun protection factor) alone, azelaic acid + hydroquinone cream, azelaic acid cream alone, topical vitamin C cream, tretinoin cream, topical tranexamic acid cream, hydroquinone + dexamethasone cream , triple combination cream (22), hydroquinone cream, hydroquinone+ hyaluronic acid cream, hydroquinone+ glycolic acid cream, hydroquinone+ glycolic acid + hyaluronic acid cream, combination of glycolic acid and klingman formulae (23), kojic Acid+ corticosteroids cream , ,klingman Formulae (hydroquinone 5%, tretinoin 0.05%, hydrocortisone acetate 1% in a cream base) ,Combination of glycolic acid and klingman formulae (24)

Oral Treatments

Ascorbic acid, Arbutin, Mulberry extract, Korean red ginseng powder, Polypodium leucotomos, hydroquinone etc (25)(26) as mentioned in table -1.

Laser treatments

Low-Fluence Nd: YAG (1,064nm) Laser, Low-Fluence QSAL (755nm) laser treatment, Treatment with picosecond laser combination (1064) and (595nm) +2% Hydroquinone cream (controlled) (27)(28).

Miscellaneous Treatments

hydroquinone vs methimazole (Topical) cream, Combinational therapy using Tranexamic acid(topical) and hydroquinone (oral), Tranexamic acid vs klingman Formulae (29)

Mechanism of Action

Above enlisted treatments of melasma show their mechanism of action by tyrosinase inhibition of competitive (eg-Flavanoids) and non-competitive type(eg-Polyphenols) by the means of various plants and non-plant derivatives like-Azelaic acid, Arbutin, Kojic acid, Hydroquinone, Hyaluronic acid, Corticosteroids, Tretinoin, Niacinamide derivatives etc.

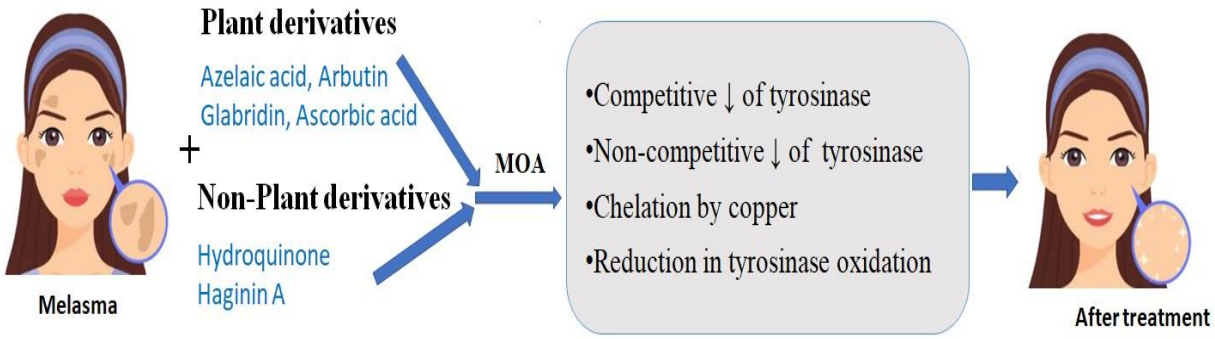

Fig-1 Mechanism of action of different anti-tyrosinase agents.

A wide range of classic herbal drugs and their phytoconstituents are given in table -1 with the categorization of each herb studies and used part in the treatment and management of melasma. Even after the presence of so many drugs, okra (abelmoschus esculentus) was introduced as an anti-melasma agent because maximum of these herbs are not easily available and are very costly for a long span of treatment. Till the time no single treatment of melasma is universally efficacious which provide the path for innovation of novel treatment measures (30).

Table -1 Phytomedicinal constituents used in the treatment of melasma

Herb	**Phytoconstituents**	**Part used**	**Study**	**References**
Liquorice	Glycyrrhizic acid, Glycyrrhizin	Root	Randomized, blinded (double)and controlled studies,	(31)((32), (33), (34), (35)(36), (37)
Chaste tree	Negundin A, [+]-lyoniresinol-3a-O-b-Dglucoside	Root	HPLC (C-18) Studies at 254nm and 330nm	(38)
Aloe vera	Aloesin, 2"-Feruloylaloesin	Leaf	Variance Analysis using one way “ANOVA”, Controlled trials	(39), (40), (34), (35) (36), (37)
Mulberry	Apigenin, umbelliferone, astragalin	Fruit	HPLC studies to determine the phenolic contents present in mulberry ethanolic extracts, RCT	(41), (31), (34), (35), (36), (37)
Ginseng	Ginsenoside, p-Coumaric acid	Root	Controlled and randomized radical scavenging activities determination	(42), (43), (44), (45)((35)

Gingko	Ginkgolide A, bilobalide	Flower	Studies of HPLC (C8 Column) Pharmacokinetic and fingerprinting regions	(46)
Neem	Oleic Acid, Azadirachtin, isomeldenin	Leaf, Bark	Controlled studies HPLC determination	(47), (31), (48)
Sandalwood	Alpha- and beta-santalol	Wood	Analysis of the cell toxicities and radical scavenging activities of Indian sandalwood oil on HaCaT cells	(49), (31), (48)
Calabura	Stigmasterol, triglyceride, α-linolenic acid	Flower, leaf, fruit	Assays to determine total phenolic content and reducing capacities were conducted	(50), (31)
Sambong	3-O-7W-Biluteolin	Leaf	Various studies like "SD, SDE, and HS-SPME'' were performed in order to determine the volatile components present.	(51)
Magnolia Bark	Magnoloside Ia, crassifolioside, magnoloside Va	Bark	Methanolic extracts of fermented bark of Magnolia officinalis was determined using HPLC	(52), (31)
Kudzu	Schaftoside, puerarin, genistin	Root	EtOAc-soluble extract was analysed to determine its anti-tyrosinase activities using DPPH assay	(53), (31)
Indian Gooseberry	Quercetin, Kaempferol, Gallic acid	Fruit	DPPH and radical scavenging assay (anion) were conducted in order to determine its anti-tyrosinase activities	(54),(31)
Turmeric	Curcuminoids	Root	Free radical scavenging activities	(55), (34)

			determination on wister rats, RCT/split-face trial	
Tea tree	Epigallocatechin gallate, epicatechin, Gallocatechin, epigallo-catechin-3-gallate (ECGC)	Leaves	DPPH free radical scavenging activity was determined by in vitro analysis, RCT trial	(56), (34)
Lotus	Pronuciferine, Armepavin	Flower	Studies were conducted on aging mice induced with D-Gal/LPS	(57),(58)
Saffron	Crocin, picrocrocin, β- carotene, safranal, flavonoids and anthocyanins	Dried stigma	TPC, DPPH and radical scavenging activities were studied	(59), (60), (61)
Sarsaparilla, Anantmul	Hemidesminine, Lupeal, vanillin	Roots	HPLC determination of the root and stem extracts of Hemidesmus indicus	(62),
Grapevine	Gallic, protocatechuic, vanillic, syringic and ellagic acids	Seeds and leafs	Spectrophotometer detection of dopamine inhibition	(63)
Spurge	Protocatechuic acid, nodakenin, 3-O-glucoside	Leave, flowers and tubers	DPPH assay and radical scavenging activities were analyzed	(64)
Lementoko	Alkaloids, glycosides, terpenoids	Leaves	Free radical scavenging activities were studied and analyzed	(65), (60)
Goosefoot	Phenolics, flavonoids, saponins	Stem, leaves and flower	Methanolic extracts were determined using HPLC in order to check the presence of flavonoids and phenols in equivalence with ascorbic acid	(66), (31), (37)
Sesame	Terpenoids and steroids	Leaves	Important phytoconstituents of	(67),(60)

			sesame were determined and analyzed using HPLC, UV and NMR	
Sugarbush	Terpenoids and steroids	Root, bark	Steroids were determined for their potency using HPLC, UV, NMR, IR etc.	(68)
Papaya	Papain, chymopapain A and B	leaves	Phenolic groups were determined using DPPH assay and radical scavenging determination	(69),(37)
Cutch tree	Catechin, catechutannic acid	Bark	DPPH analysis and radical scavenging determination	(70)
wolf's bane	Triterpene, essential oils, fatty acids, thymol, pseudoguaianolidesesquiterpene lactones	Flower	3β,16β-Dihydroxy-21a-hydroperoxy-20[30]-tariaxasten was determined using HPLC, UV analysis	(71), (31)
Dragon Plant	Isobutyl and piperidiyl	Leaves	Blinded studies of B16 cells of mouse melanoma cells	(72)
Soya bean	Kunitz-type trypsin inhibitor	Seed	RCT and controlled studies were performed	(73), (34), (37)
Mitnan	Genkwadaphnin, gnidicin	Leaves, Stem and flower	Controlled studies were performed	(74), (37)
White Birch	Phenolics, flavonoids, tannins, saponins	Bark, leaves	Blind folded studies were performed	(75)
Redwood	Homoisoflavanone, sappanone A	Woods	DPPH assay and radical scavenging activities were determined	(76)
Beautyberry	carnosol and carnosic acid	Leaves	HPLC and UV determination of	(77), (60)

			phenolic extracts was done	
Safflower	palmitic acid, palmitoleic acid	Seeds	Spectrophotometric determination of melanin inhibition	(78)
Seagrape	Titratable acid Ascorbic acid and gallic acid	Root, bark and wood	DPPH assay was performed	(79), (37)
Eddoe	Colocasinol A	Root and bark	HPLC and UV determination of Colocasia extracts	(80), (31)
Azarole	vitexin-200-O-rhamnoside	Leaf	Rosaceae extracts were determined using HPLC, UV	(81)
Chinese Juniper	Amentoflavone-7-O-D-glucoside	Fruit	Radical scavenging activities were determined using DPPH analysis	(82)
Tunhoof	Germacrene D Ursolicacid, oleanic acid	Stem	Spectrophotometric determination of phenolic extracts	(83), (37)
African mangosteen	Amentoflavone 3βhydroxyeupha-5	Bark	RCT and controlled studies were performed	(84)
Wood Violet	Vitamin C, methyl salicyte	Leaf	Blind folded and controlled studies were performed	(85),(37)
Passion fruit	Piceatannol	Seed	DPPH analysis and radical scavenging activities were determined	(86)
Stewartia	deoxystewartianol-40 -O-arabinoglucoside	Bark and fruit	Phenolic extracts were determined using HPLC, UV	(87)
Coco grass	Valencene camphene	Rhizomes	DPPH assay was performed	(88)
Chinese mulberry	Flaniostatin	Fruit	Radical scavenging activities were determined using split face trial	(89)

Okra

Okra (abelmoschus esculents) commonly known as “Lady finger” also known as “gumbo is very rich in the concentrations of vitamins, minerals, flavanols, polyphenols, quercetin and its derivatives because of which it shows excellent antioxidant, anti-cancerous, anti-microbial, anti-ulcerative and anti-hyper lipidemic properties .Its Genetic diversity can be studied using RAPD marker techniques where RAPD stands for (Rapid amplified polymorphic DNA).Okra’s easy availability, cost effectiveness, simple handling, high stability and high anti-inflammatory properties makes it a potential alternative for the treatments of melasma and it is marked with multiple roles in drug delivery systems which are mentioned in figure-3 and okra’s pharmaceutical approaches are mentioned in table-2.Constituents based analysis of each part of okra which will become the basis of future research are as follows (90-93)(16)

Flower=Immuno stimulating property (94), Highest number of flavonoids (prevent the diseases related to reactive oxygen species (ROS) (95), polysaccharide and polyphenols are present (96). **Flower Petals**=Two Anthocyanins are found namely- Cyanidin 4’-glucoside and Cyaniding 3-glucosido-4’ glucoside (97). **Location of flowers**=Axillary parts, Fruiting time=2-3 days (98). **Pods**=Rich in pectin (Polysaccharide [shows excellent DPPH radical scavenging activities (99)] = xyloglucans, xylans, and celluloses), composed of galacturonic acid chains (100). Pod mucilage of okra contains phenolic content ranging between 4.66 to 49.93 mg GAE/g and flavonoid content ranging between 8.18–18.72 mg CE/g (101). Nutritional value reducing agents are present in pods such as saponins, oxalates etc which affects the overall bioavailability of Calcium, iron and Zinc (102). **Okra seeds**=oil containing linoleic acid (90), procycanidin B2, B1 and rutin, Polyphenols (29.5%) and polysaccharides (14.8%), Isoquercitrin (2.067%), quercetin-3-O-gentiobiose (2.741%), Flavonoids (5.35%) (103),(104) **Pulped seeds**=Catechin, epicatechin additional to procycanidin B2 and rutin (105)and oligomeric catechins (106). **Dried Okra seeds**= No nutritional benefits, **Fresh seeds**= Beta carotene highest quantity (107).

Note-Overall nutrient and antioxidant activity of seeds can be increased by roasting seeds at 1600 degree Celsius for around 10-60 min whereas nutritional values of seeds increase by soaking and blanching for hours before processing but on other hand decreases antioxidant activity of seeds (105).

Mucilage=Mucilage is rich in polysaccharides (galacturonic acid, galactose, 44 glucose and glucuronic acid and rhamnose (108)) because of which it is thick and slimy in nature (109). It is widely used as binding, emulsifying, suspending and film coating agent (96). Low concentration of mucilage can be used as binder (110). Mucilage is widely used as polymer and is of great importance in CR/SR drug delivery systems (111). Characterization of okra mucilage is done on the basis of morphology, swelling, viscosity and flow properties (112). **Okra skin**=Polyphenols (1.25%) and polysaccharides (43.1%) (103),(104)where Bulk Density (kg/m3) and Tapped Bulk Density (kg/m3) of Sun-dried Okra is 800 and 950 (113).

Extraction Procedures of mucilage

For alcohol- soluble residues-Freeze dry the Okra pods for at least 24 hours followed by the separation of seeds and calyx.

Use aqueous ethanol (70%v/v) for the extraction of mucilage.

20g of pods or seeds were extracted out using 70%v/v ethanol at 40 degrees celsius/ hour.

For alcohol-insoluble residues-Wash the alcohol-insoluble residue with acetone followed by air drying

20 g of insoluble residue is extracted out using 0.1 M phosphate buffer at pH 6.0 at 70-degree celsius.

Centrifuge the residues at 25 degrees celsius for 30 min (108).

Where**,** Oven method can be used to determine the water content of seeds at 105 °C ± 3 °C for 24 h

weigh the seeds after 24h to determine seeds dry weight or follow the procedure as given in figure-2 (114) (111)

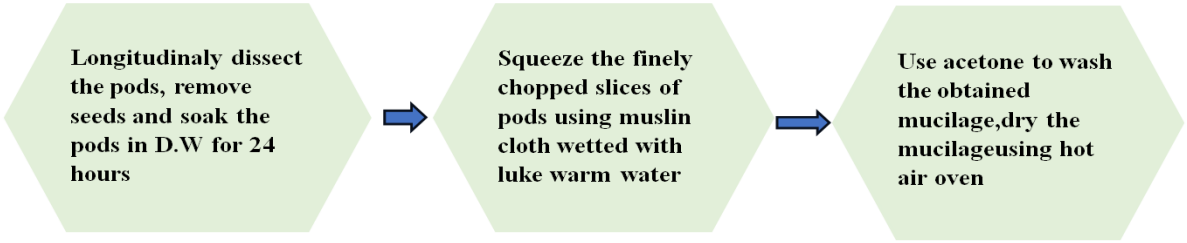

Figure- 2 Extraction procedure of mucilage from okra

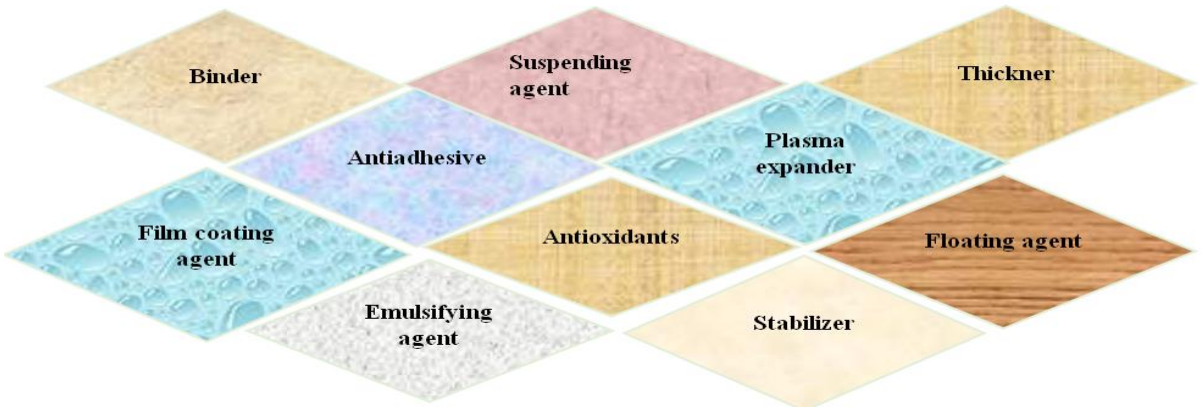

Figure- 3 Role of okra in drug delivery system

Evaluation of Okra parts

Fourier transform infrared spectroscopy (**FTIR**)-To determine pectin composition in sample (100)

Response Surface Methodology (**RSM**)-To determine extraction conditions of Phenol and its derivatives.

Thin Layer Chromatography (**TLC**)-Reveals information about phenolic content of the sample like quercetin and catechin.
Ferric Reducing Antioxidant Power Assay (**FRAP**)-Determines the antioxidant and radical scavenging capacities of extracts (115)
Note-Okra mucilage extracts showed higher antioxidant activities in comparison to the okra seeds and skin extracts (116).
Size Exclusion Chromatography (**SEC**)-Assessment of polysaccharides after extraction as well as the properties and stability of emulsions are also determined by SEC (117).
2, 2-diphenyl-1 picrylhydrazyl Assay (**DPPH**)-Determines the antioxidant activities of extract (118),
Total Phenolic content Assay (**TPC**)-Determines the tannins, flavonoids, and polyphenols. Saponins and terpenoids ratios and antioxidant activities within the sample (119),
Colorimetric Assay (**CA**)-Anti-Tyrosinase activities were determined using colorimetric assays,
Heating cooling Method and Franz diffusion System- Stability and permeability of extract are determined by this method (120)
Liquid Chromatography (**LC**) and Mass Spectrometry (**MS**)-Determination and identification of polyphenols (121).

Table- 2 Available formulations of okra

	Formulations	Properties	Characterization	Observations	References
1.	Okra alginate beads	These beads show sustained, controlled release and are sensitive toward pH degradation.	By SEM (Scanning electron microscopy) and FTIR (Fourier transform infrared spectroscopy)	64.19 ± 2.02 to 91.86 ± 3.24 % entrapment efficiency	(122)
2.	ZnSo4 linked diclofenac sodium-Okra alginate beads	Shows Controlled release pattern and	SEM, FTIR and P-XRD ((Powder X-ray diffraction)	89.27 ± 3.58% entrapment efficiency and show 43.73 ± 2.83%, pH=1.10 ± 0.07, Bead size=1.38 ± 0.14 mm	(123)
3.	Okra hydrogel	Shows Sustained release pattern	By SEM, XRD (X-ray diffractometry) and FTIR	Aqueous Solution intrinsic viscosity =5.31 dL/g and 8.38 dL/g	(124)

4.	Mucoadhesive Okra Polymers	Shows the property of Mucoadhesion when comes in the presence of moisture.	FTIR, DSC (Differential scanning calorimetry) and XRD, Surface methodology	Swelling index (107.89 _ 1.99%), 99.68% release profile	(125)
5.	Okra fruit derived Nano emulsions	Rich in natural steroids like phytosterol	FTIR, Dissolution studies	134.7 nm=particle size, 0.512= polydispersity index and -26.72 mV=Zeta potential	(126)
6.	Silica based Okra gums	Gum shows high Mucoadhesion, High porosity and fast disintegration rate after silica incorporation	FTIR, DSC, Hardness, friability, Weight variation, Disintegration test and dissolution studies	Swelling index=205, pH=6.1	(127)
7.	Okra polymers	Okra polymers show sustained release of drug	FTIR, SEM, XRD, DSC, UV	Size=250.91 ± 16.22 to 462.10 ± 23.85 µm, Swelling index=1.35 ± 0.05 and 3.20 ± 0.03, Entrapment efficiency=55.70 ± 3.55–94.11 ± 4.50%	(112)
8.	Okra gum tablet matrix	Matrix shows drug-polymer compatibility and showed sustained release drug patterns	FTIR, NMR, Viscosity analysis, P-XRD and elemental analysis	DCSmax=0.604 ± 0.011and %Grafting=644.1	(128)
9.	Silver nanoparticle of okra	Highly stable, controlled release of drug, effective in chemical reduction	UV, FTIR, TEM (Transmission electron microscopy), EDX (Energy dispersive X-ray	Nanoparticle average size=16nm and face centered cubic structure, Centrifugation	(129),(130)

			spectroscopy), SPR (Surface plasmon resonance)	=360 rpm for 15 min, FTIR peaks=1632 for leaf, 1626 for stem, and 1653 for pod	
10.	Okra modulated-green iron nanoparticle	Effect in gene transformation of okra	UV-Visible spectroscopy, SEM, TEM, LSCM (Laser scanning confocal microscopy), PCR (Polymerase chain reaction)	Centrifugation speed=800 rpm, Time=5h	(131), (130)
11.	Bioflocculant extracted green-Iron nanoparticles	Effective in purification of okra extracts	FTIR, XRD, SEM, AFM (Atomic force microscopy), TEM, DLS (Dynamic light scattering), UV	Iron nanoparticle size=50nm, Lead removal efficiency =91.45%, contact time= 30 min , Dosage=0.2 g/L , Temperature= 30 degree Celsius ,pH=6,UV Visible range=200-350nm	(132), (130)

Available marketed formulations analysis-

4% Hydroquinone (HQ) till time found out to be the most potent treatment of all but show high mutagenicity and exogenous ochronosis. So it can be easily replaced with 5% methimazole(topical) (133)(134),20% azelaic acid (135),35% gallic acid (136), triple combination cream (TC) with 2 corresponding intense pulse light treatments (137) ,where 8 weeks application of TC can cure hyperpigmentation and 6 months TC application prevent relapses (138).Note-These treatments are very costly and causes high side effects because of their long term treatments, so they can't become the potential candidates in treatment and management of melasma.

Okra analysis-

On conducting each part analysis of okra, okra seeds have reported 10 times higher concentration of flavanols and almost 15 times higher concentration of catechin as compared to okra skin, which makes okra very much capable of producing high anti-melanogenic effects against hyperpigmentation (139).On the other hand okra mucilage extracts showed higher

antioxidant activities in comparison to the okra seeds and skin extracts (116). Varieties of okra like shakti Shivam and bhendi Anjali showed superior seed viability as per the researches of databases like ScienceDirect, Elsevier, PubMed etc, (140) where ethanolic extracts of okra pods (141) showed excellent antioxidant properties (142).Mark that herbs with tyrosinase inhibition capabilities show good skin whitening properties too, which makes okra a suitable candidate for the cosmeceutical industries also (143).

Conclusion –

In this review we enlisted a wide variety of herbal and synthetic treatments in the management of melasma but these were marked with high cost, instabilities, high degradation, skin irritation and are majorly associated with high side effects and high rate of relapses. Introduction of okra as a potential candidate in the treatment and management of melasma can become the basis of future studies of okra as anti-melasma agent because of the high concentration of flavanols, catechin and anthocyanin etc present in it which ultimately leds to the excellent antioxidant and anti-tyrosinase properties of okra .It reduces the oxidative stress and can cure the melasma from its roots, it may take time but okra's cost effectiveness and easy availability will not become hurdle.

Ethical Issues

Not applicable.

Conflict of Interest

The author declares that there is no conflict of interest.

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