Newer therapy options in the management of melasma

Role of 4-n butylresorcino

Melasma

- Very common condition that develops exclusively on the exposed areas of the face.
- Basic mechanisms involved in the pathogenesis of this difficult to treat disorder is still not very well known.
- Despite wide range of depigmenting agents available, the treatment of melasma is often unsuccessful and disappointing
- Still a challenge for dermatologists

J Cutan Aesthet Surg. 2012 Apr-Jun; 5(2): 93-103.

Appearance

- Greek, '*melas*' – black
- Common, acquired, circumscribed hypermelanosis of sun- exposed skin.
- Symmetric, hyperpigmented macules with irregular, serrated, and geographic borders.
- Common locations are the cheeks, upper lips, chin, forehead, also other sun-exposed areas

Indian J Dermatol. 2012 Jul-Aug; 57(4): 324-326.

Indian Epidemiology

- Incidence of melasma in pregnant women in India it was found to be nearly 10%

B Dwari, S Palaian, A Poudel, S Prabhu. *Clinical profile and management pattern of melasma patients in Western Nepal: A Hospital Based Study*. The Internet Journal of Dermatology. 2008 Volume 7 Number 1.

Indian Epidemiology

- Fitzpatrick type III-VI common
- Dark haired women more susceptible
- Male to Female ratio 1:9 (Indian study ~ 20% males with melasma)
- Genetic
- UV & Visible light (infrared light)
- Estrogen receptors on melanocytes in 1/3 rd women
- Cosmetic (Fragrance) & phototoxic drugs
- Dermatology and Therapy. December 2014, Volume 4, Issue 2, pp 165-186

Causative factors

- Amongst males, melasma patients appeared to be sun-exposed and having some family history.
- Mustard oil application may also contribute
- Melasma considered as photocontact dermatitis (Verallo-Rowell). Photoallergens are present in products used daily in much lower concentrations than those used in photopatch tests. Overtime cumulative exposure may reach irradiancetest dose.
- Development of photosensitivity (Asymptomatic suberythematous dermatitis) by about 30-40yrs followed by post inflammatory hyperpigmentation.

- J Drugs Dermatol. 2008 Feb;7(2):149-56.

Causative factors

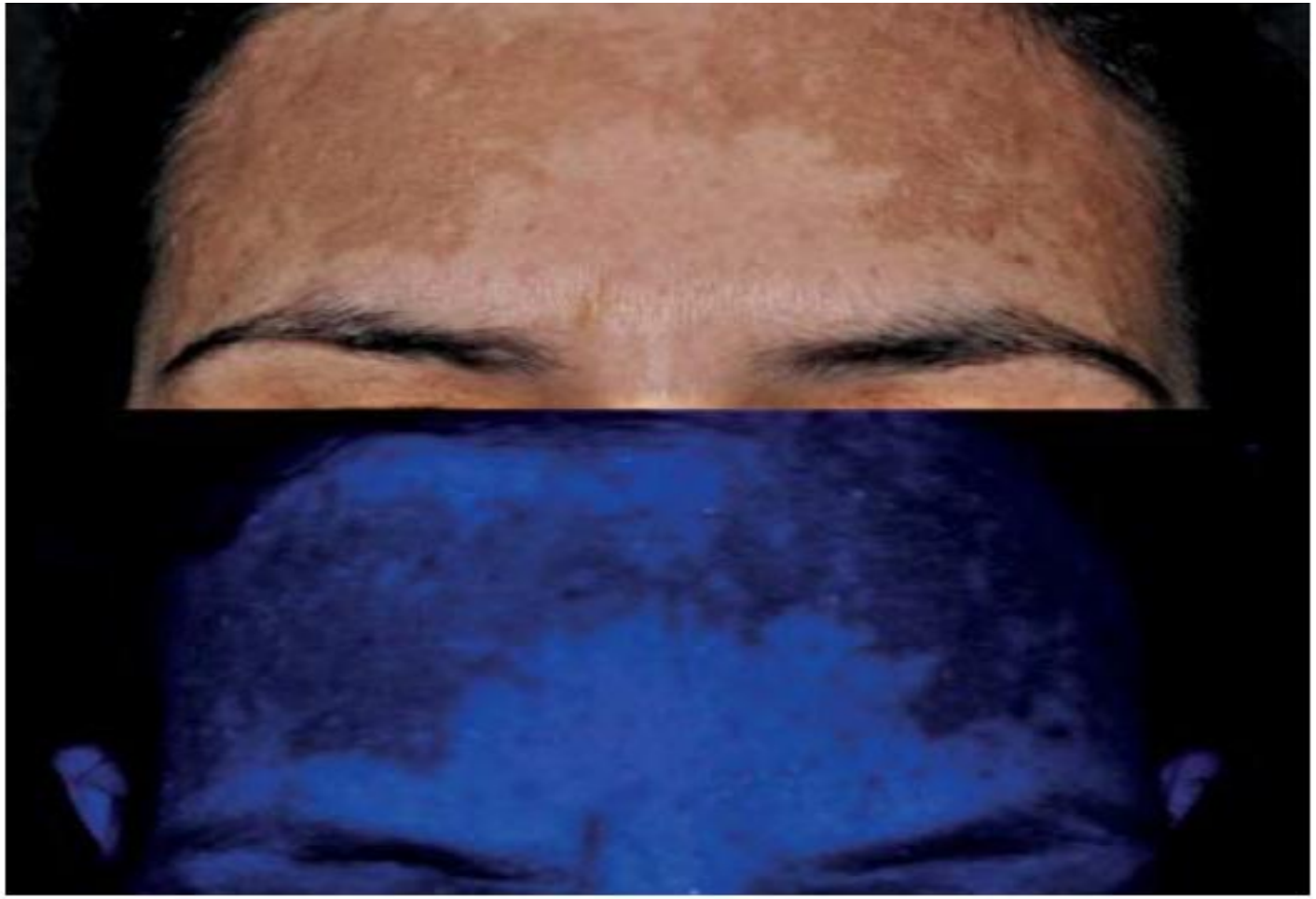
- Light : UVA, UVB, visible light
- Hormone : pregnancy, contraceptive pill
- Drug : Dilantin, anti-malarial drug, Tetracycline, Minocycline
- Cosmetic : perfume, color
- Genetic
- Malnutrition : Liver dysfunction, B12 def.

Factors incriminated	Supportive evidence(s) proposed
Sunlight	Typical affection of the sun exposed areas. Exacerbation of the lesion by light.
Hormonal	Frequent association with oral contraceptives, pregnancy and endocrine dysfunction.
Genetic	Occurrence of familial cases.
Toxic (ingredients in cosmetics)	Females more commonly affected.
Drugs	Characteristic affection of the face, the part of the body which is frequently exposed to cosmetics. Development of a similar type of facial pigmentation following phenytoin therapy

Classification : Histological

- by Wood's light examination / physical examination:

Type of melasma	Clinical features
Epidermal	▪ Well-defined border ▪ Dark brown colour ▪ Appears more obvious under black light ▪ Responds well to treatment
Dermal	▪ The most common type ▪ Ill-defined border ▪ Light brown or bluish in colour ▪ Unchanged under black light ▪ Responds poorly to treatment
Mixed	▪ Combination of bluish, light and dark brown patches ▪ Mixed pattern seen under black light ▪ Partial improvement with treatment



Comparison between photography with visible light (top) and with the use of Wood's lamp (bottom) highlighting the limits of the frontal macules of melasma

An Bras Dermatol. 2014;89(5):771-82.

Relevance

- Estrogen may play a role in melasma induction(OCP, HRT, pregnancy)
- Pregnancy induced melasma will recover after some months

Summary of histopath findings in melasma

Epidermis:

- Overactive melanocytes
- Barrier function weakend
- Disruption of basal layer

Dermis

- Dermal vascularity increased
- Greater actinic damage
- Mast cells increased
- Prostaglandin synthesis increased

Principles of therapy

- Broad spectrum sunscreens
- Inhibition of tyrosinase activity
- Uptake and distribution of melanosomes
- Melanin and melanosome degradation

Classification of depigmenting agents and their mechanism of action

Stage of melanin synthesis	Deposition	Active molecules
Before melanin synthesis	Tyrosinase transcription	Tretinoin, c-2 ceramide
	Tyrosinase glycosylation	$PaSSO_3Ca$
	Inhibition of plasmin	Tranexamic acid
During melanin synthesis	Tyrosinase inhibition	Hydroquinone, mequinol, azelaic acid, kojic acid, arbutin, deoxyarbutin, licorice extract, rucinol, 2,5-dimethyl-4-hydroxy-3(2H)-furanone, *N*-acetyl glucosamine, resveratrol, oxyresveratrol, ellagic acid, methyl gentisate, 4-hydroxyanisole
	Peroxidase inhibition	Phenolic compounds
	Reactive oxygen species scavengers	Ascorbic acid, ascorbic acid palmitate, thiotic acid, hydrocumarins

Dermatol Ther (Heidelb) (2014) 4:165–186

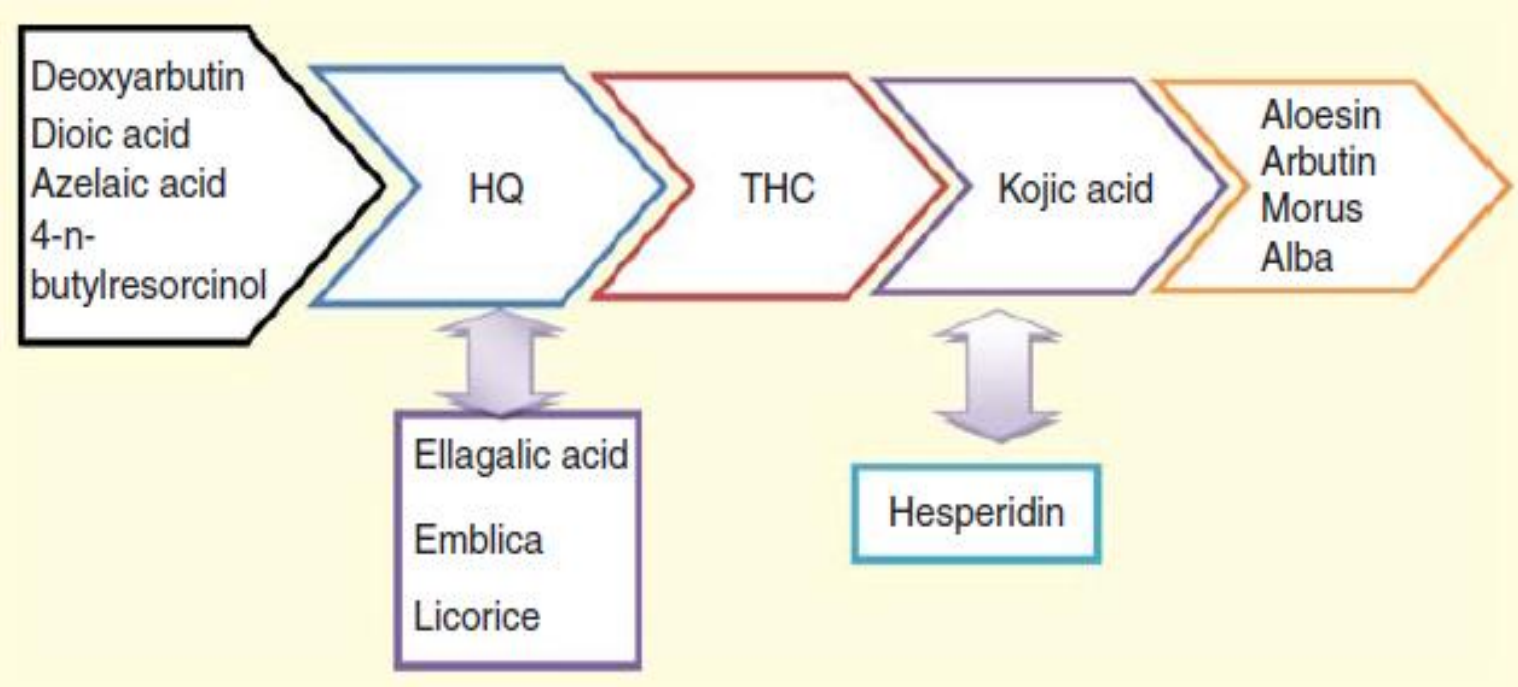
Classification of depigmenting agents and their mechanism of action

After melanin synthesis	Tyrosinase degradation	Linoleic acid, α-linoleic acid
	Inhibition of melanosome transfer	Niacinamide, serine protease inhibitors, retinoids, lecithins, neoglycoproteins, soybean trypsin inhibitor
	Skin turnover acceleration	Lactic acid, glycolic acid, linoleic acid, retinoic acid
	Regulation of melanocyte environment	Corticosteroids, glabiridin
	Interaction with copper	Kojic acid, ascorbic acid
	Inhibition of melanosome maturation	Arbutin and deoxyarbutin
	Inhibition of protease activated receptor 2	Soybean trypsin inhibitor

Dermatol Ther (Heidelb) (2014) 4:165–186

Pharmacologic therapy

- Hydroquinone
- Tretinoin
- Corticosteroids
- Kojic acid
- Sunscreens
- HQ+Tretinoin + Steroid
- Mequinol +tretinoin
- Newer agents (4-n-butyl resorcinol)



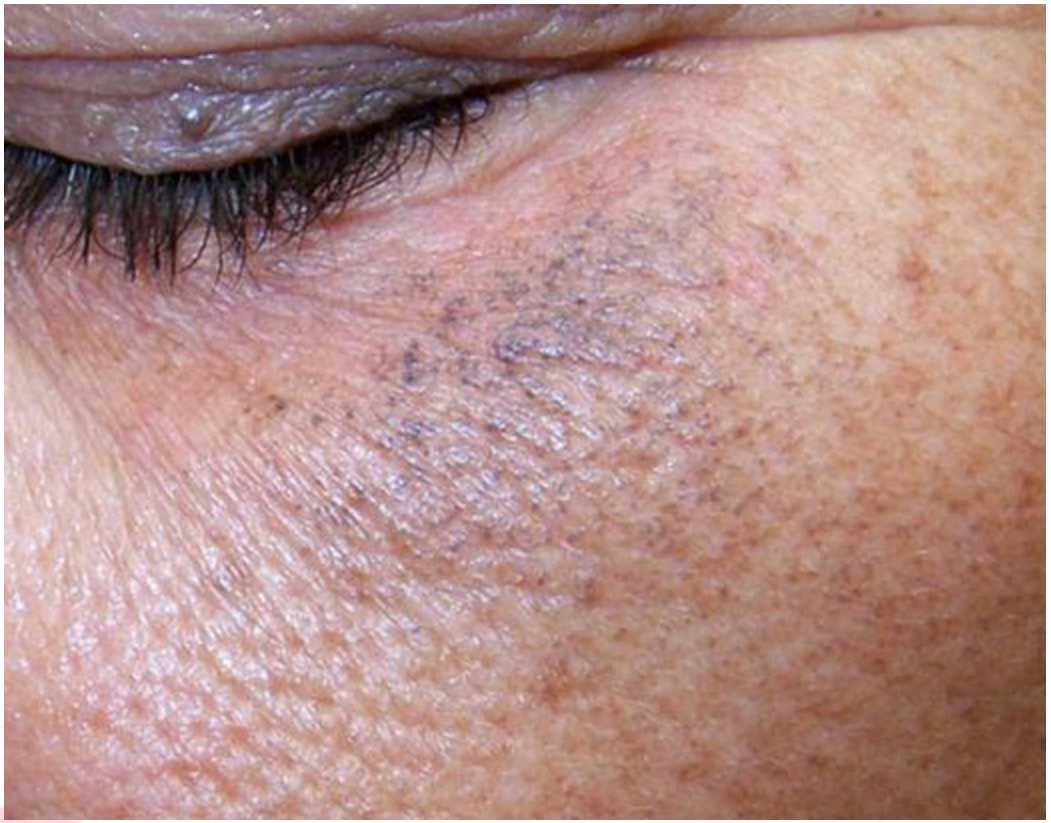
A comparative analysis of the relative efficacy of depigmenting agents based on *in vitro* and *in vivo* data [47–49,56–61]. Compounds are arranged from left to right from highest to lowest efficacy. The drugs below are equivalent in efficacy to the drugs listed above.

Hydroquinone

- 2%-4% has been widely used for melasma therapy.
- Inhibits the conversion of dopa to melanin by inhibitin theactivity of tyrosinase.
- May interfere with DNA and RNA synthesis, degrade melanosomes, and destroy melanocytes.

Hydroquinone Side Effect

- Exogenous ochronosis. Blue-gray discoloration of the skin with characteristic pin-point, caviar-like papules



Alternative therapies

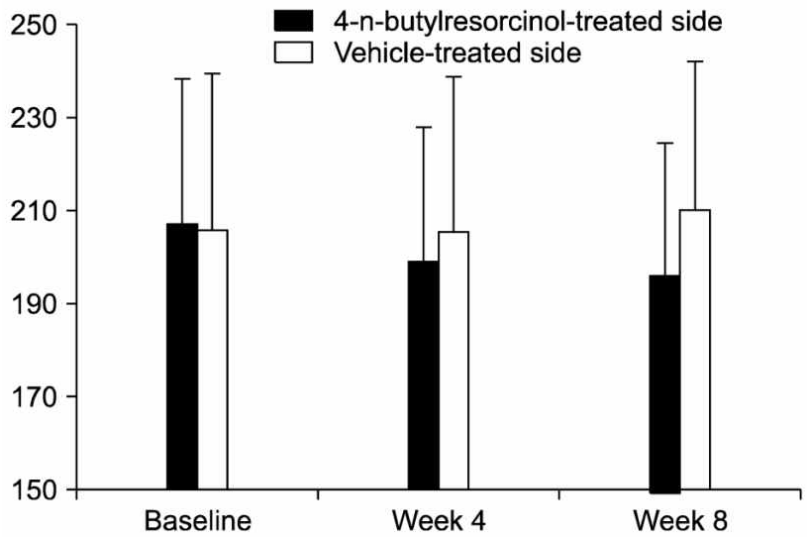
Therapeutic agent
Tranexamic acid
Vitamin C
Vitamin E
Soybean extract
Topical liquiritin
Licorice extract
Gigawhite
Bearberry extract
Pepper mulberry extract
Arbutin
Indomethacin
Niacinamide
Nicotinic acid
4-*N* butylresorcinolmercury
Melawhite

Botanical extracts being used for the treatment of melasma

Plant extract	Active component	Mechanism of action
Grape seed extract	Proanthocyanidin	Antioxidant
Orchid extract	Contain flavonoids	Antioxidant
Aloe vera extract	Aloin	Melanin aggregating effects
Pycnogenol	Procyanidins, polyphenolic monomers, cinnamic acid	Antioxidant
Marine algae extract		Inhibition of tyrosinase
Cinnamic acid		Inhibition of tyrosinase
Flavonoids		Antioxidant
Green tea extracts	Epigallocatechin-3-gallate	Antioxidant? inhibition of tyrosinase
Coffee berry	Chlorogenic acid	Antioxidant
	Proanthocyanidins	
Mulberry extract	Contain methanolic extracts	Inhibition of dopa oxidase activity of tyrosinase
		Superoxide scavenging activity
Soy	Phospholipids	Inhibition of melanosome transfer by inhibiting PAR-2 activation
	Essential fatty oils	
	STI	
	BBI	
Licorice extract	Glabridin	Inhibits UVB induced pigmentation
Umbelliferone	7-hydroxycoumarin	Absorbs UV light, antioxidant
Boswellia	Boswellic acid	Anti-inflammatory, pro-apoptotic, mechanism not clear

4-n-butylresorcinol

- Resorcinol derivative
- Inhibitory effect on both tyroosinase and tyrosinase related protein-1
- Hypopigmenting efficacy and safety of 0.1% cream was tested in 20 patients, in a randomized, double blind, vehicle controlled study
- Melanin index (Mexameter) showed significant decrease in all patients. Rapid efficacy and well tolerated



(Ann Dermatol 22(1) 21~25, 2010)

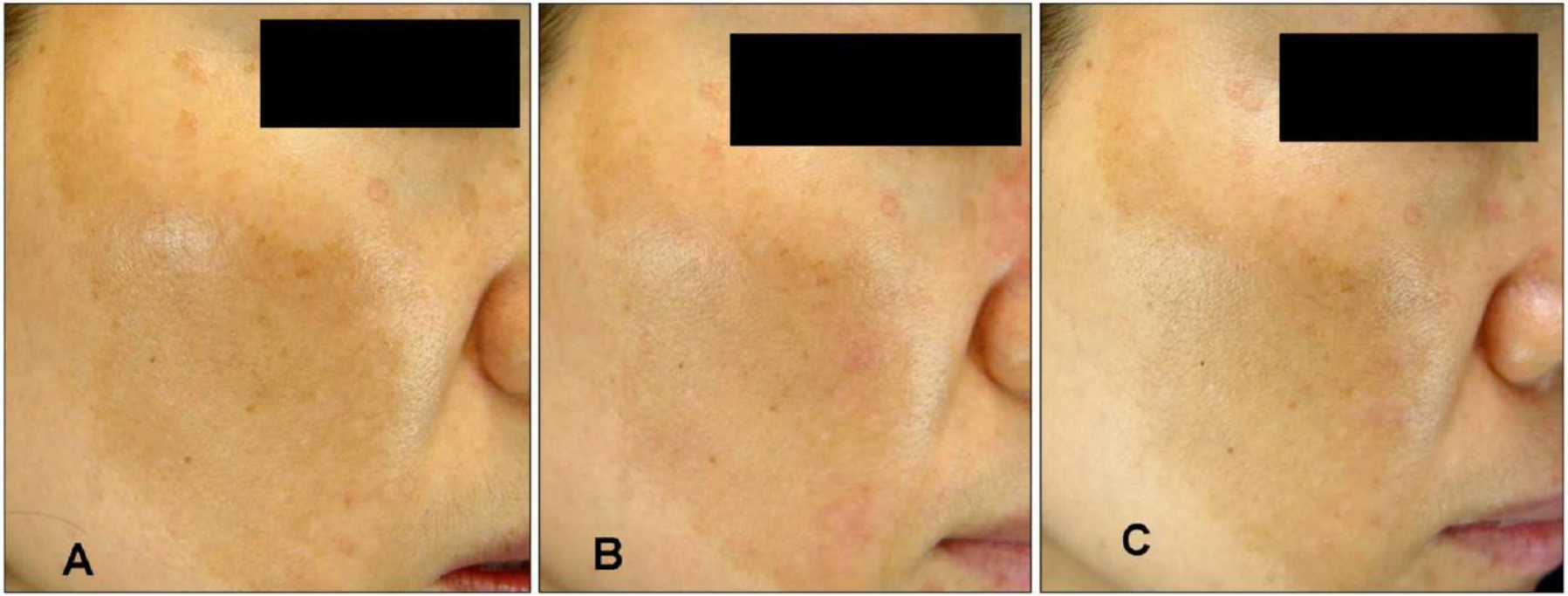


Fig. 2. Patient 1: A 41-year-old woman with melasma was treated with 4-n-butylresorcinol 0.1% cream, and her melanin index (MI) decreased from 221.33 to 210.33 (−11.00). The clinical presentation at baseline with the MI: 221.33 (A), after 4 weeks with the MI: 215.33 (B) and after 8 weeks with the MI: 210.33 (C).

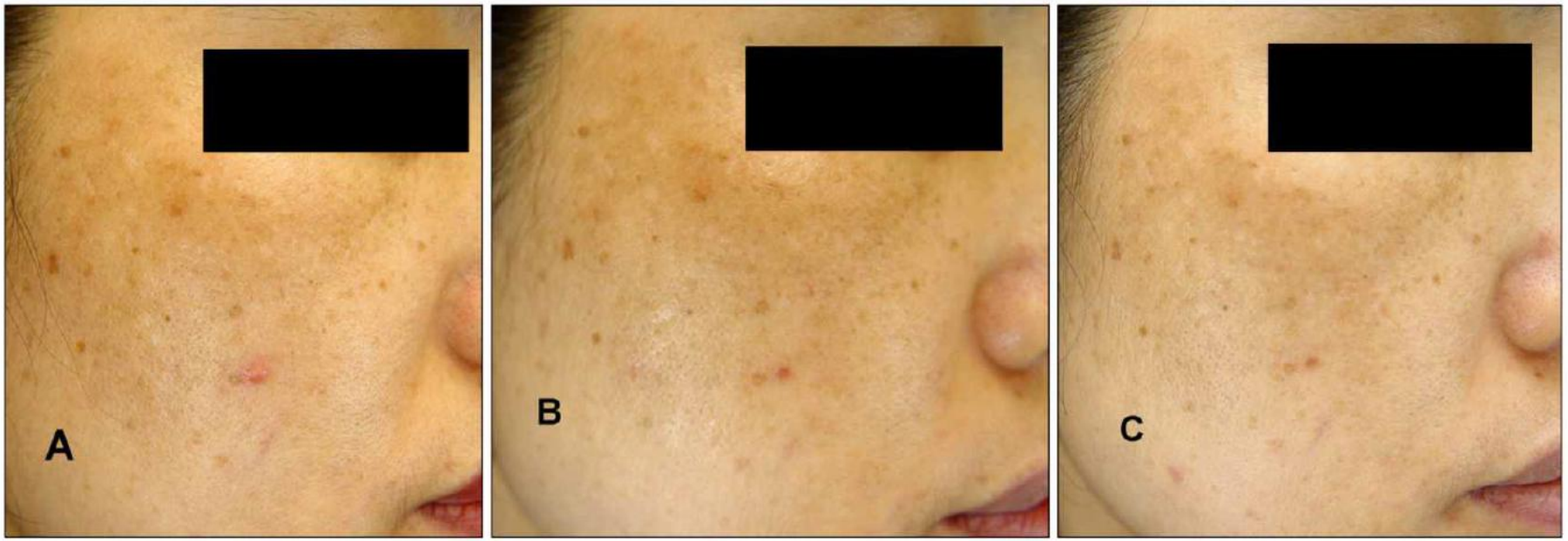


Fig. 3. Patient 2: A 46-year-old woman with melasma was treated with 4-n-butylresorcinol 0.1% cream, and her MI decreased from 234.00 to 208.00 (−26.00). The clinical presentation at baseline with the MI: 234.00 (A), after 4 weeks with the MI: 213.00 (B) and after 8 weeks with the MI: 208.00 (C).

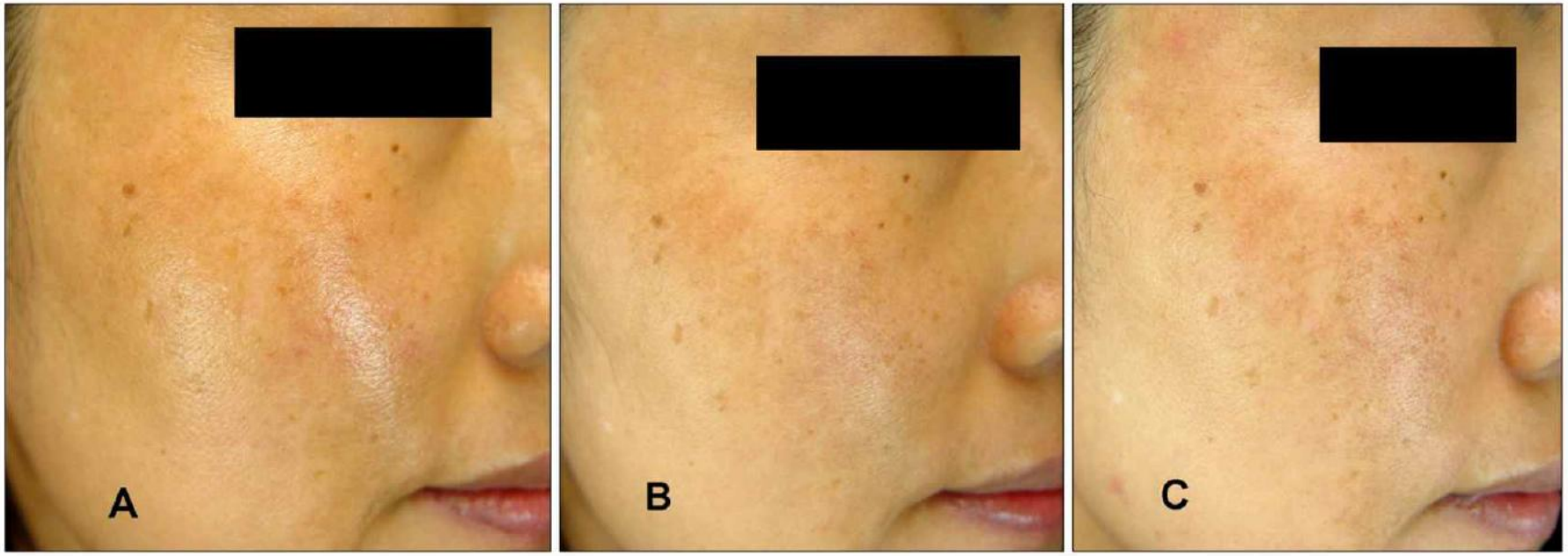


Fig. 4. Patient 3: A 44-year-old woman with melasma was treated with 4-n-butylresorcinol 0.1% cream, and her MI decreased from 223.00 to 189.33 (−33.67). The clinical presentation at baseline with the MI: 223.00 (A), after 4 weeks with the MI: 197.33 (B) and after 8 weeks with the MI: 189.33 (C).

4-n-butylresorcinol

- Novel, anti-melanogenic compound
- In 18 week, placebo controlled study, 4-n-butylresorcinol showed significant improvement in post laser pigmentation
- In 84% melasma patients, 0.3% 4-n-butylresorcinol serum was found to be effective.
- Another recent randomized double blind study on 28 patients showed 0.3% serum to be significantly effective after 12 weeks, based on colorimetric and clinical assessment.

Akasaka T et al. Topically applied 0.3% 4-n-butylresorcinol decreases pigmentation after laser therapy. Environ Dermatol 2009. :9. 11-15

Nishinihon J Dermatol. 1991. 61. 813-819

Khemis A et al. Evaluation of efficacy and safety of rucinol serum in melasma patients, a randomized contorlled trial. Br J Dermatol. 2007. 156. 997-1005

4-n-butylresorcinol

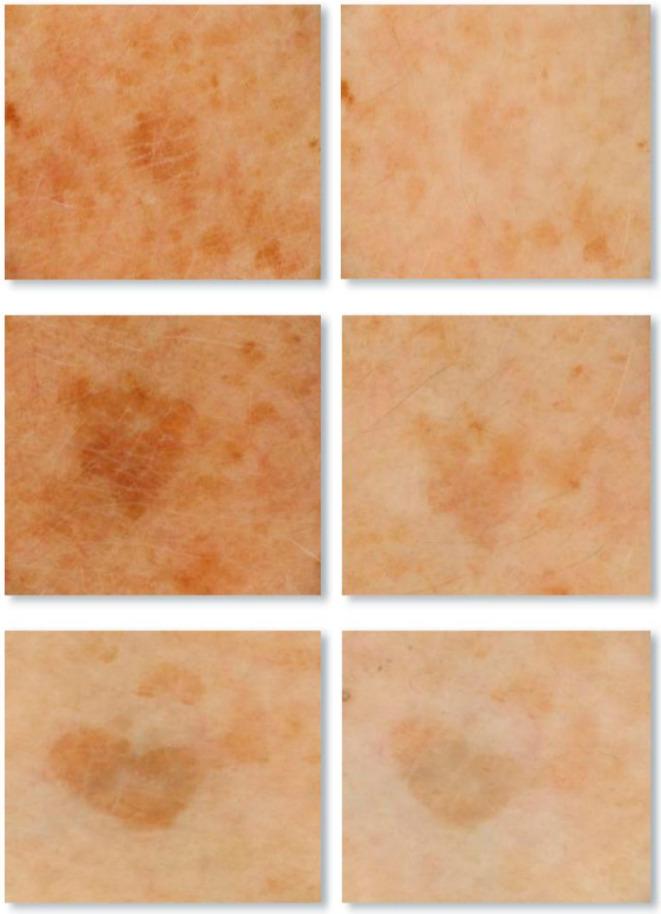
- Arbutin and hydroquinone only weakly inhibit human tyrosinase with a half maximal inhibitory concentration (IC(50)) in the millimolar range. By far the most potent inhibitor of human tyrosinase is 4-n-butylresorcinol with an IC(50) of 21 µmol/L.
- In vivo efficacy confirmed in clinical studies.
- Reduced visibly the appearance of age spots.
- Was more effective than 4-hexylresorcinol and 4 phenyl ethylresorcinol.
- In vitro and in vivo data has proven the high inhibitory capacity on human tyrosinase activity, exceeding by far the potency of hydroquinone, arbutin and kojic acid.
- A very valuable active compound for the management of pigmentation disorders.

J Eur Acad Dermatol Venereol. 2013 Jan;27 Suppl 1:19-23.

CLINICAL STUDY

- Arbutin only weakly inhibit human tyrosinase with an effective concentration for 50% inhibition (EC50) in the millimolar range
- However, is 4-n-butylresorcinol

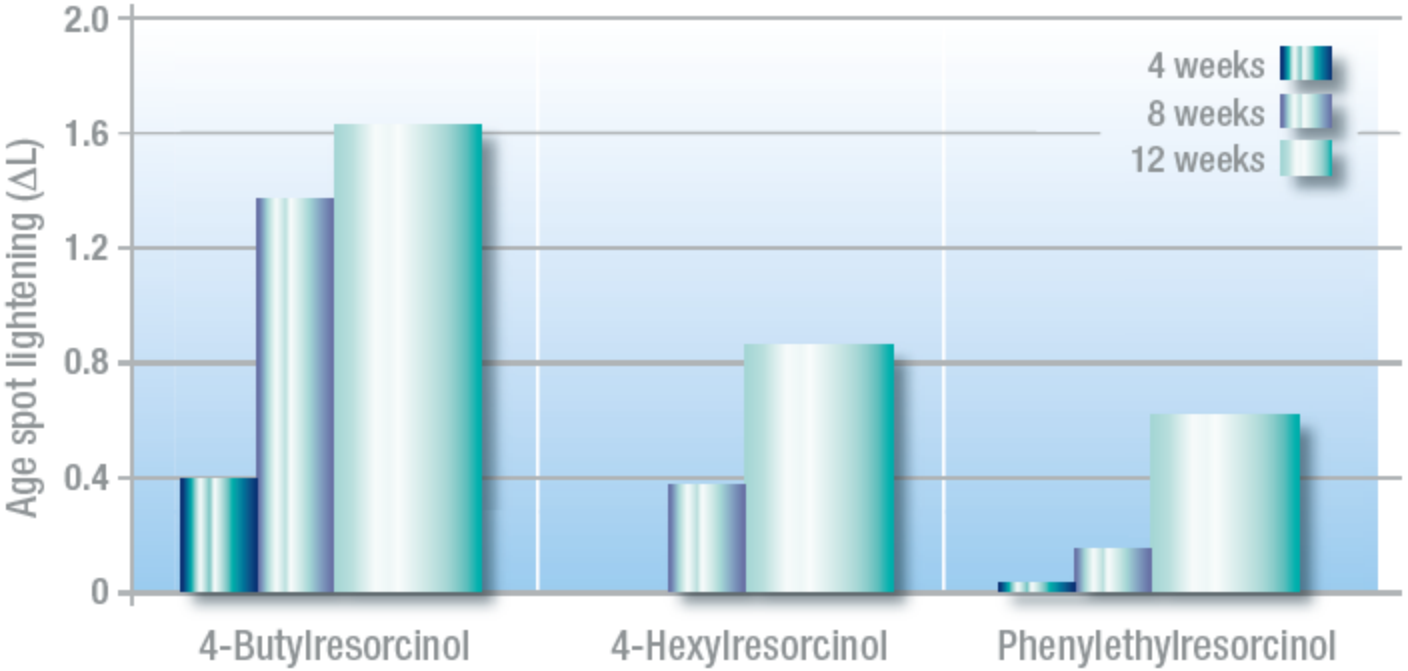
is more potent with an with an EC50 of 21µM (fig. 4).



Epi-Flash photographs reveal visible improvement in the appearance of age spots after 12 weeks of treatment with 4-butylresorcinol.

Ref:- Winder AJ, Harris H. Eur. J. Biochem. 1991, 198:317-26

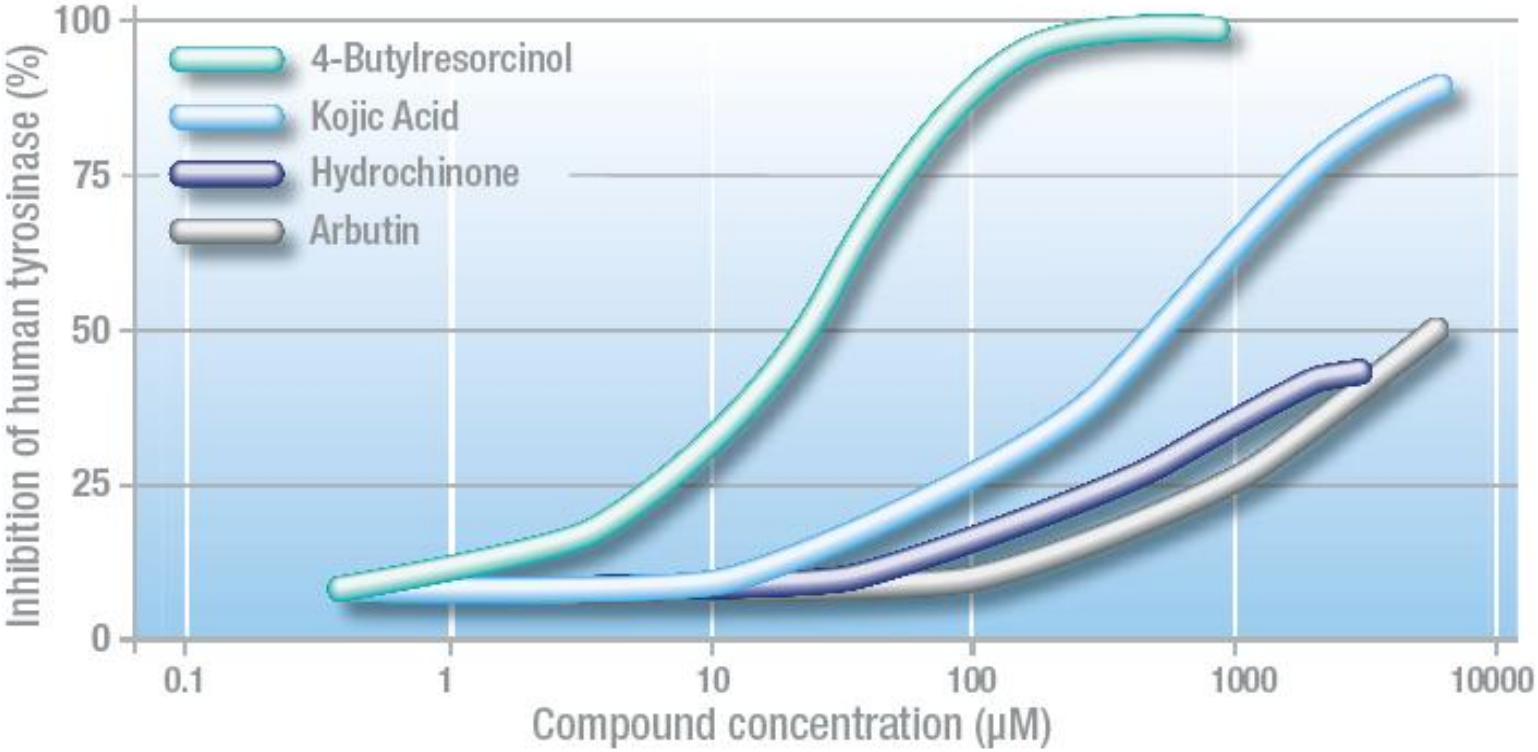
CLINICAL STUDY



Elderly subjects treated age spots twice daily either with a formula containing 4-butylresorcinol, 4-hexylresorcinol or phenylethylresorcinol. Within eight weeks 4-butylresorcinol significantly reduced the appearance of age spots while 4-hexylresorcinol or phenylethylresorcinol showed significant effects after 12 weeks (all in comparison to vehicle).

Ref:- Winder AJ, Harris H. Eur. J. Biochem. 1991, 198:317-26

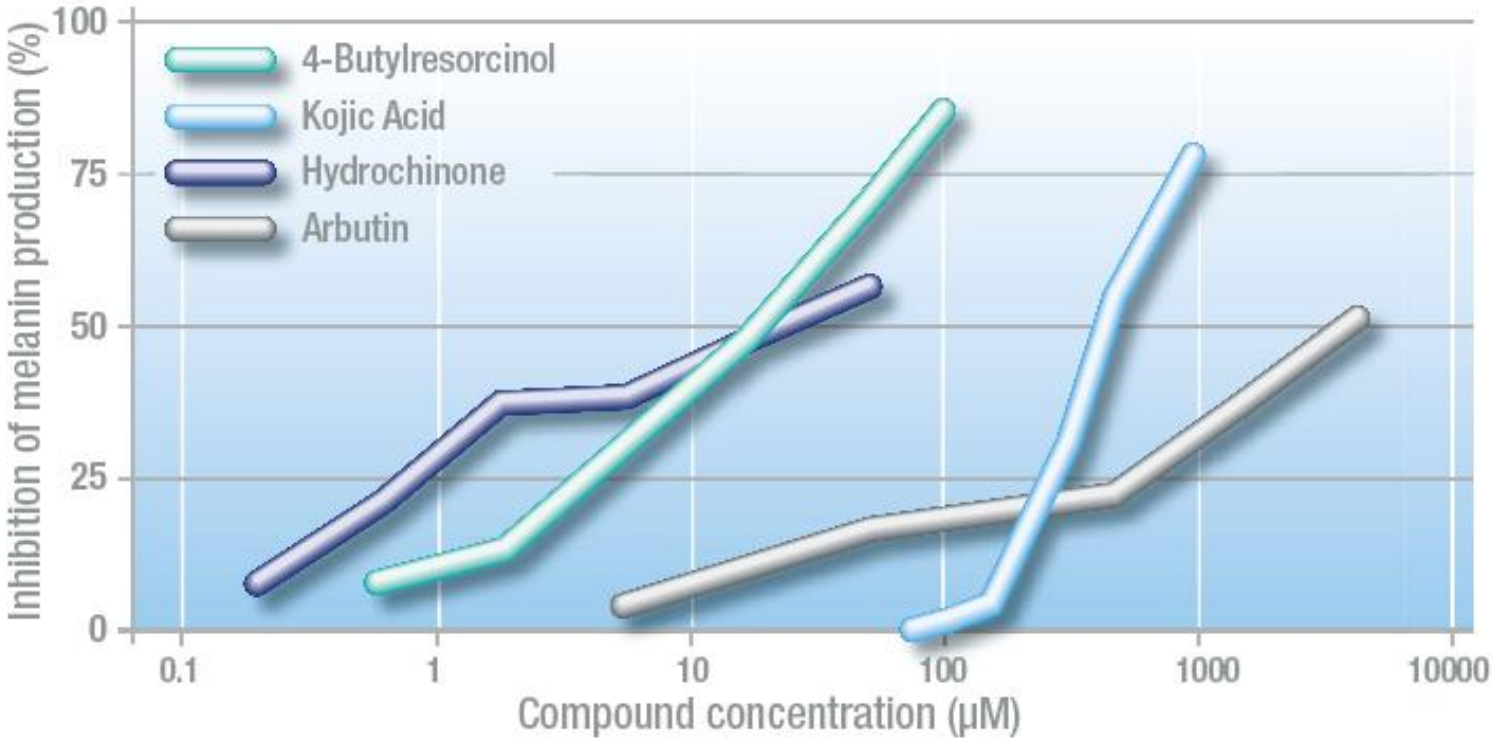
TYROSINASE ACTIVITY



Tyrosinase activity assay: 4-butylresorcinol is a highly effective inhibitor of human tyrosinase with an EC50 of 21µM. Kojic acid was more than twenty-times less potent (EC50 = 500 µM). Arbutin and hydrochinone are only poor inhibitors of human tyrosinase with an EC50 in the millimolar range.

Ref:- Winder AJ, Harris H. Eur. J. Biochem. 1991, 198:317-26

EFFICACY



Arbutin showed only marginal efficacy on melanin production in skin models with an EC50 for inhibition of > 5000 µM. Kojic acid inhibited with an EC50 > 400 µM. Interestingly, hydrochinone inhibited melanin production in melanoDerms® with an EC50 around 40 µM, pointing towards a mechanism different from tyrosinase inhibition. 4-butylresorcinol was the most potent inhibitor with an EC50 of 13.5 µM.

Ref:- Winder AJ, Harris H. Eur. J. Biochem. 1991, 198:317-26

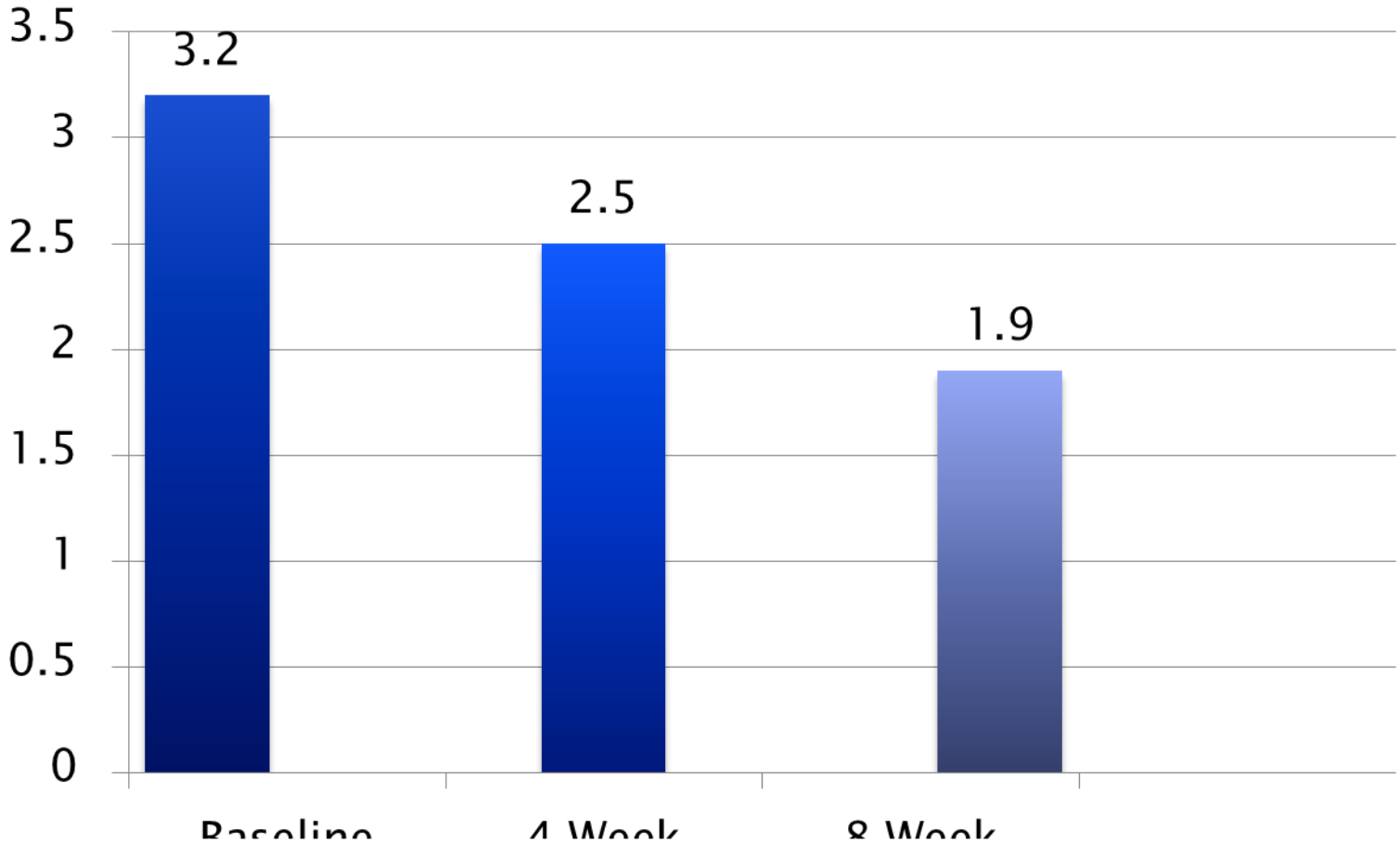
Onetone study

Investigators	Designation	Institution
Dr.Madan Mohan Dr.Ashok Jaiswal	Professor Professor & HOD Dept. Dermatology	Dr.B.R.Ambedkar Medical College (BRAMC); Bangalore, India
Dr.Adarsha Gowda Dr.Sharath Kumar	Assc. Professor Professor & HOD Dept. Dermatology	Kempegowda Institute of Medical Sciences (KIMS); Bangalore, India

- Total number of subjects enrolled : 52
- All the patients completed the study. No drop outs

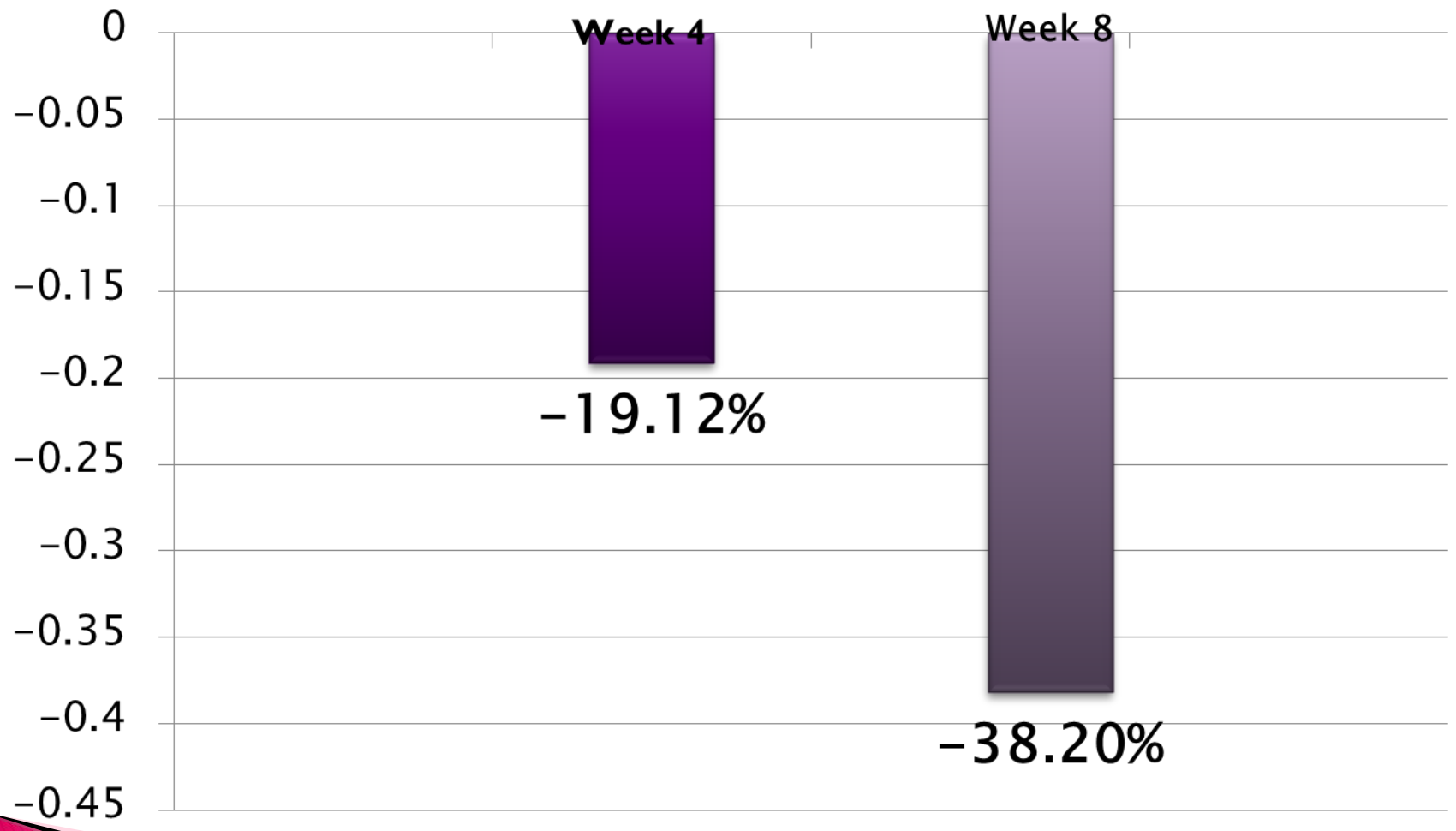
Demographic Data	
➢ Male	9%
➢ Female	91%
➢ Average Age	38.5 ±7.8 years
➢ Occupation	Majority were housewives (41%) & rest were students, nurses and laborers

Changes in MASI SCORE



Gradual reduction in the MASI score over 8 week study period which was found to be statistically highly significant (P < 0.001)

% Changes in MASI SCORE



Changes in MASI Score was statistically highly significant (P < 0.001)

SAFETY ISSUES of ARBUTIN/ HYDROQUINONE

- Arbutin in a natural and organic material – not safe skin whitener
- The reason for this is that when it is broken down in the body, it produces "hydroquinone . In other words, the synthesis and how it reacts to the body is the same. In fact, the chemical responsible for inhibiting melanin is broken down the same way regardless of what the two chemicals are labeled.
- Arbutin is nothing more than a watered down version of hydroquinone and those willing to abuse it may see the same side effects.
- .

SAFETY ISSUES of ARBUTIN/ HYDROQUINONE

- Exogenous ochronosis with the use of hydroquinone has been reported in dark-skinned patients, in particular South African women who frequently use very high concentrations of hydroquinone over large surface areas.
- Hydroquinone is used extensively in North America, there have only been about 30 reported cases of exogenous ochronosis from hydroquinone use in North America.
- Adverse reactions from hydroquinone use include irritant and allergic contact dermatitis, and nail discoloration.
- Postinflammatory hyperpigmentation may occur from the contact dermatitis.
- Hypopigmentation of the normal skin surrounding the treated areas may also occur. These usually resolve with the discontinuation of the hydroquinone treatment.

ADVANTAGES OF n-BUTYL RESORCINOL

- 4-n-butylresorcinol is a recognized skin lightening ingredient that has quite a few studies backing up its effectiveness at **inhibiting tyrosinase as well as melanin synthesis**.
- In a split-face study involving people with melasma, a pigmentation correcting cream containing 0.1% NBR significantly decreased the melanin load within the melasma legions in 8 weeks. It also demonstrated little to no adverse effects.
- Using skin lighteners or having a skin lightening regimen that attacks melanogenesis at different stages (enzyme production, melanocyte to keratinotyctes) produces better results. Using a product like Creams/lotions containing NBR can kill two birds with one stone, **since the ingredient NBR can inhibit both steps in melanogenesis effectively and gently**.
- These formulations can be used as an **all over skin lightener** and a melanin controller for **hyperpigmentation**, discolorations, freckles and **melasma**. The powerful effects of NBR are complimented by plant extracts and light weight base that is perfect for all skin types.

Dosage

- Minimum effective dosage of Skin lightening actives in formulation

1. Kojic Acid:- 1%
2. Arbutin:- 3%
3. Hydroquinone:- 2%
4. **n-Butylresorcinol :- 0.3%**

References

Maeda, K.; Inoue, Y.; et.al. . *J. Jpn. Cosmet. Sci. Soc.* **2003**, *27*, 257-268 (in Japanese).

Maeda, K.; Hatao, M. *J. Invest. Dermatol.* **2004**, *122*, 503-509.

Interventions – Scope

- Cryosurgery
- Microdermabrasion
- Chemical peels TCA, GA, Salicylic acid
- LASER
- IPL
- Dermabrasion

Laser treatment for melasma

- Target chromophore is melanin
- Should destroy melanocyte in hair follicle
- Good in dermal and mixed melasma
- Effective?

Sunscreen

- Most Indian patients dont agree with sunscreens because of oily sticky perception. Chemicals sunscreens absorb light energy and release heat as exothermic reaction (may causes heat on face).
- Physical sunscreens do not release heat but whitening on face is a disadvantage. May mix with calamine lotion or zinc to minimize these effects

Triple combination with FA 0.01%

J Am Acad Dermatol. 2010 Jun;62(6):962-7.

Continuous therapy followed by a maintenance therapy regimen with a triple combination cream for melasma.

Grimes PE[1], Bhawan J, Guevara IL, Colón LE, Johnson LA, Gottschalk RW, Pandya AG.

OBJECTIVE:

We sought to determine the efficacy and safety of continuous therapy followed by a maintenance treatment regimen during a period of 24 weeks with a TC cream containing hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%.

METHODS:

Seventy patients with melasma were treated with a TC cream daily for 12 weeks, after which, if clear or almost clear, they applied the cream twice per week for 12 more weeks. For patients who were not clear or almost clear after 12 weeks, daily treatment was continued.

RESULTS:

In all, 25 patients completing the study per protocol were treated daily for 24 weeks (cohort A); 6 patients were treated daily for 12 weeks followed by 12 weeks of maintenance therapy (cohort B); and 21 patients were treated daily for 12 weeks, relapsed during the maintenance phase, and returned to daily dosing (cohort C). Pigmentation was significantly reduced at weeks 12 and 24 and global melasma severity improved at week 24 in cohorts A and C compared with baseline. Adverse events occurred in 53% of patients and were primarily mild in severity.

LIMITATIONS:

This was an open-label trial.

CONCLUSION:

About half of patients treated with a TC cream for melasma were able to begin maintenance therapy twice per week after 12 weeks; however, relapses occurred in most of these patients, requiring resumption of daily therapy. The cream is safe in the treatment of moderate to severe melasma for up to 24 weeks when used intermittently or continuously. Significant reductions in melasma severity scores were seen at weeks 12 and 24 when compared with baseline scores in all evaluable study groups.

CONCLUSION

- Many substances described as inhibitors of tyrosinase are very effective inhibitors of mushroom tyrosinase but rather poor inhibitors of human tyrosinase. NBR has shown to be a very powerful chemical moiety for inhibition of human tyrosinase.
- The present in vitro and in vivo studies prove the high inhibitory efficacy of 4-n-butylresorcinol on human tyrosinase activity, exceeding by far the potency of hydro - chinone, arbutin, and kojic acid. The resulting clinical improvement of skin hyperpigmentations renders 4-n-butylresorcinol a valuable active for pigmentation disorders.

Ref:- Winder AJ, Harris H. Eur. J. Biochem. 1991, 198:317-26

Prognostic factors

- Dark haired person
- Family history
- More than 2 years duration
- History of procedures ~ Lasers peels
- Ochronosis features
- History of steroid self use

My approach to treatment

- UVA+++ sunscreen in all
- First line: Hydroquinone+tretinoin+kojic acid OR Hydroquinone+glycolic acid+kojic acid OR Hydroquinone+4-n-butylresorcinol combination
- Second line: Glycolic acid peels added +/- oral tranexamic acid
- Third line: Fluocinolone or hydrocortisone containing triple combinations

My approach to treatment

- Lifelong maintenance
  - With glycolic acid+/-low strength hydroquinone and sunscreens
  - With non-hydroquinone agents (resorcinol/kojic acid compounds) and sunscreens

Conclusion

End notes

Thank you!

How to approach?

History and examination

↓

Sunscreens

↓

Mometasone based triple cream for 4 – 8 weeks + Glycolic peels

↓

Fluocinolone or hydrocortisone based triple creams + peels 3 – 6 months

↓

Oral antioxidants vitamin C ,E , pine bark extract

↓

Fluocinolone based triple creams twice a week for 3 – 4 mths

↓

Non hydroquinone non steroid creams kojic acid, vitamin c ,arbutin etc