Mohamed et al. BMC Chemistry (2025) 19:104
https://doi.org/10.1186/s13065-025-01404-6

BMC Chemistry

RESEARCH

Open Access

Thiadiazole chitosan conjugates as a novel cosmetic ingredient for rinse-off hair conditioners: design, formulation, characterization and in silico-molecular docking studies

Ahmad E. Mohamed[1], Walid E. Elgammal[2], Ahmed G. Ibrahim[2], Hamdy M. Dawaba[3,4], Eman S. Nossier[5,6] and Aya M. Dawaba[7*]

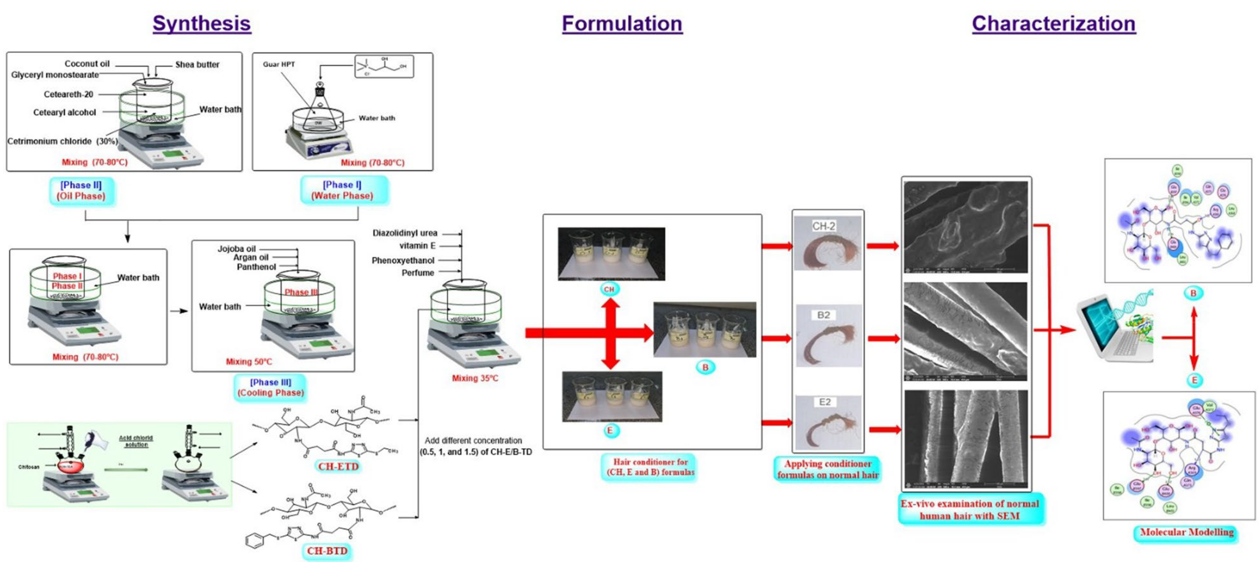
Abstract

Recently, chitosan derivatives, as eco-sustainable and renewable products, have been recorded to be highly effective toward cosmetics with potent biological activity. The main core of this research is to develop an organic hair conditioner (OHC) based on two chitosan-thiadiazole conjugates, chitosan-(ethylthio-thiadiazole) (CH-ETD) and chitosan-(benzylthio-thiadiazole) (CH-BTD), with natural fragrances. A series of nine OHC formulae were prepared (CH1-CH3 for chitosan based OHC, E1-E3 for CH-ETD based OHC, and B1-B3 for CH-BTD based OHC) and characterized based on their visual examination, pH, thermal stability, dirt dispersion, moisturizing time**,** percentage of solid content, hair irritation, rinsing, combing, and the luster. The results showed that the pH values of all OHC formulae were 4.2–4.7 which is considered acceptable to avoid skin irritation. A distinctive film surrounds each individual hair shaft in the CH-ETD and CH-BTD treated groups when compared to control hair without the application of hair conditioner under a scanning electron microscope SEM with a magnification power of 100 µm. Additionally, every single hair shaft is clearly covered, and the control group exhibited noticeable hair issues that were not observed in the treated groups, which showed no signs of tangling. Due to the end-use performance properties of the formulated hair conditioner products, it can be concluded that the formulas of (CH, E2, and B2) were the best efficacy; hair easier to style, detangle the hair, retain moisture, not be very thick, not cause irritation or inflammation, minimize frizz, and create a protective barrier on the hair. These findings collectively validate the potential of CH-ETD and CH-BTD based formulations coupled with natural perfumery as a transformative approach to hair care, aligning with consumer preferences for both efficacy and environmental sustainability. Furthermore, in this work, docking studies have been conducted to provide theoretical proof about the significant roles of chitosan and keratin in hair growth and cosmetic applications (skin).

Keywords Thiadiazole chitosan derivatives, Hair treatment, Polymers, Formulation, Natural fragrances, Organic cosmetic products, Rinse-off conditioners, Molecular docking

*Correspondence:
Aya M. Dawaba
ayadawaba365.el@azhar.edu.eg; aya.dawaba@yahoo.com
Full list of author information is available at the end of the article

Graphical Abstract



Introduction

The marketing of cosmetic products with a focus on innovations towards green chemistry and environmental sustainability. In general, the green cosmetics for personal care products consist of natural and organic sources [5]. Sustainability focuses on enhancing organic components with herbal and natural ingredients, avoiding silicones, sulfates, phthalates, and mineral oils. This approach promotes a preference for safer and healthier products. Consumers are becoming more aware of the hygiene and health benefits of personal care products, and they are gravitating towards natural and organic products, [50, 71]. Among these products, organic hair conditioners hold a significant place in the realm of cosmetic formulations, offering a harmonious blend of natural ingredients and advanced science to enhance hair health and appearance.

Chitosan is a biopolymer; it's extracted from numerous marine sources, including crab, lobster, and prawns. It is considered a polysaccharide because it's derived from chitin by partial or full deacetylation. It is widely used in the medical field due to its chemical, cosmetic, and pharmacological properties [30, 78]. Chitosan has many advantages; the three most significant benefits are biocompatibility, biodegradability, and nontoxicity [11, 33]. Despite these properties, chitosan suffers from the disadvantage of insolubility in all organic solvents except in acidic medium (pH $<$ 6) such as acetic acid. Where the medium becomes neutral or basic, it precipitates. This limitation restricts some of its potential applications [27, 30]. Previous studies have addressed this issue by the chemical modification to enlarge the spectrum of its cosmetic and biomedical applications [27, 35, 41, 45, 46].

Chitosan and chitosan derivatives have been used in various cosmetic applications, including hair and skin care products such as shampoos, conditioners, body lotions, sunscreens, and creams. They serve as safe alternatives to the synthetic ingredients due to their antimicrobial properties and high moisture retention ability [37, 74, 75]. Chitosan has also been used for encapsulating natural ingredients in certain cosmetic products [7, 65]. Additionally, incorporating chitosan and its derivatives into hair conditioners offers benefits such as detangling hair, nourishing it, and enhancing manageability [32].

Keratin is a protein found largely in the hair, skin, and nails of humans and other animals. It is classified as strong, fibrous protein and known to be resistant to scratching and torning. In addition, it is an important protein in the integumentary system involving hair, skin, and nails. It helps to keep the structure of the body strong. Keratin is present the epidermal layer of skin, which is the outermost layer and, strangely, plays a role in skincare and possesses unique qualities that may be beneficial.

Many articles reported the potential risks associated with using cosmetics containing synthetic ingredients over an extended period. Some synthetic ingredients, such as fragrances or preservatives, can cause skin irritations, which can range from mild redness and itching to more severe conditions like dermatitis or eczema [51, 53]. Some studies suggest that certain synthetic chemicals found in cosmetics, such as parabens or phthalates, may have endocrine-disrupting properties. These substances can potentially interfere with the body's hormonal balance and have been associated with reproductive issues and certain types of cancer [22, 29].

Previously, we modified chitosan, as a natural biopolymer, with ethyl/benzyl thiadiazole moieties, and the biological studies approved high activity against the growth of *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, and *C. albicans* with minimum inhibitory concentration (MIC) values in the range of 25–200 μg mL^{-1} [45, 46]. Our search of scientific databases revealed that the use of chitosan derivatives in hair conditioner formulations has not been reported. The novelty of this work lies in investigating, for the first time, two new chitosan derivatives (referred to as CH-ETD and CH-BTD for ethyl and benzyl thiadiazole derivatives, respectively) as natural ingredients in hair conditioner formulations. We hypothesize that incorporating these ingredients into the formulation will make hair easier to style and reduce the effort required when combing, particularly when the hair is wet. Furthermore, a detailed docking study with keratin was conducted. To provide additional insight on chitosan and keratin cosmetic applications especially for skin and hair care (i.e. hair growth and skin brightening).

Experimental work

Materials and instrument specifications

The two chitosan-thiadiazole conjugates (CH-ETD and CH-BTD) were synthesized and characterized as described in our published paper [45, 46]. Xanthan gum, stearic acid, guar Hydroxypropyltrimonium chloride, isopropyl myristate, cetearyl alcohol, glyceryl monostearate, monopropylene glycol, ceteareth-20, PEG-7-glyceryl Cocoate, shea butter, Jojoba oil, argan oil, coconut oil, cetrimonium chloride 30%, D-Panthenol, vitamin E, Biocrol C2, phenoxyethanol, Diazolidinyl urea were obtained from Nerol for Manufacturing and Trading Company, Egypt. The fragrance ingredients were purchased from Ventós, Lluch Essence, and Indukern, Spain. Brookfield Digital Viscometer DV-III + ULTRA, TEM, Italia. Elcometer 1800 density cup stainless steel, volume 100 cc, UK. Scanning Electron Microscope (SEM), model Prisma E, ThermoFisher SCIENTIFIC, UK.

Formulation procedure for rinse-off deep conditioner

The main objective of this application is to prepare a unique deep hair conditioner that is more efficient and devoid of sulfates, alcohols, mineral oils, and silicones. A deep conditioner contains a higher percentage of oils and has a higher viscosity with an oil-in-water emulsion (O/W). The conditioning base is formed by an aqueous phase and an oily phase. The active ingredients are moisturizing, emollient, humectant, cationic surfactant, botanical extract, emulsifier, stabilizer, thickener, antioxidant, preservative, and fragrance [12]. The formulations were prepared as follows: (1) hydroxypropyltrimonium chloride was dispersed in the distilled water by using a magnetic stirrer at 75–80 °C until complete hydration and homogeneity, then cetrimonium chloride 30% was added to the hot water dispersion. (2) In a separate container, a mixture of glyceryl monostearate, ceteareth-20, cetearyl alcohol, shea butter, and coconut oil was melted at 75 °C. (3) Then the melted wax was poured into the hot water phase and mixed well, then it was left to reach 50 °C. (4) Following that, a mixture of jojoba oil, argan oil, and panthenol was added, and the overall mixture was cooled to 35 °C. (5) Diazolidinyl urea, phenoxyethanol, vitamin E, and fragrance were added to the previous mixture in step 4. 6) To the mixture obtained in step 5, a 0.5–1.5 ml solution of chitosan or its derivatives (CH-ETD and CH-BTD) (2%) in glacial acetic acid was added to the base of the hair conditioner. There are nine formulas prepared with different concentrations (0.5, 1, and 1.5 ml) and designated as follows: CH-1, CH-2, and CH-3 for chitosan, E1, E2, and E3 for CH-ETD, and B1, B2, and B3 for CH-BTD, respectively. The formulation composition of hair conditioner is shown in Table 1, and photographic pictures are shown in Fig. 1.

Formulation of fragrance

The fragrances are classified according to the odor characteristics of each aroma chemical. There are three structural parts of a pyramid graph (triangle); the head of the

Table 1 Composition of Rinse-off deep-hair conditioner

Category	Ingredients	W/W %
Foundation	Distilled Water	Up to 100
Emollient	Coconut oil	1.00
	Argan oil	1.00
	Jojoba oil	2.00
	Shea butter	3.00
	Panthenol	0.50
Thickening agent	Cetearyl alcohol	6.00
	Glyceryl monostearate	2.00
	Guar-HPT	0.30
Antioxidant	Vitamin E	0.50
Surfactant	Cetrimonium chloride	2.50
	Ceteareth-20	2.00
Film-forming	CH-E/B-TD solution	(0.5, 1, 1.5)
Preservative	Phenoxyethanol	0.50
	Diazolidinylurea	0.50
Natural Perfumery	Fragrance	0.60

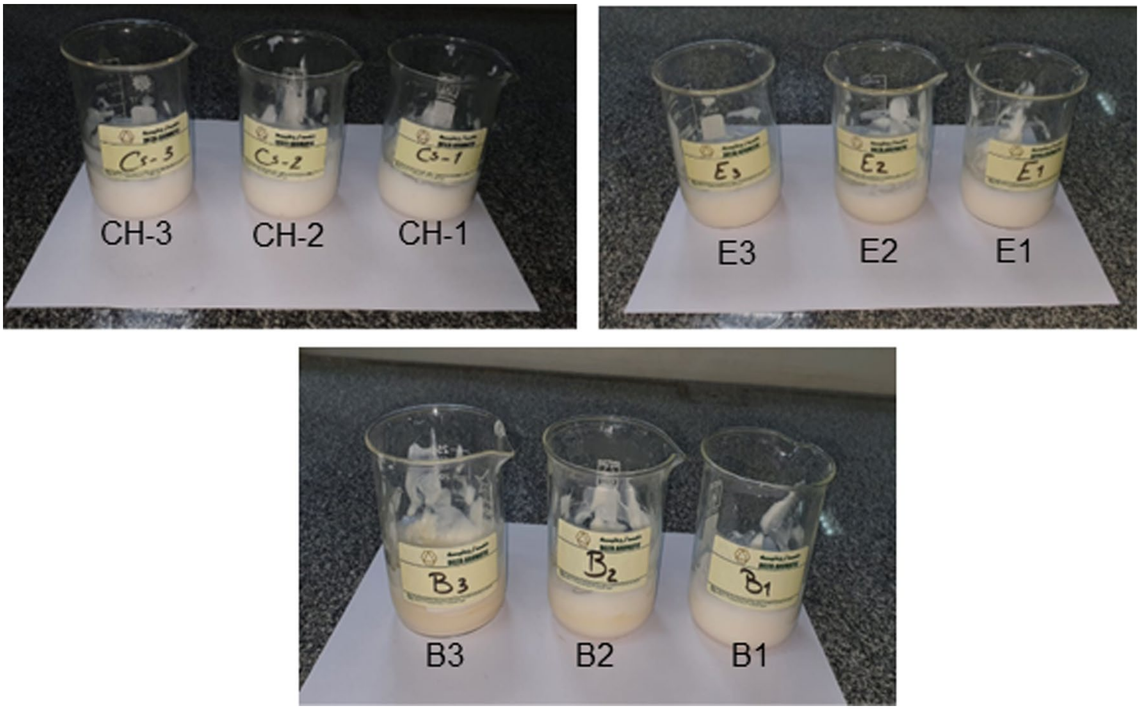


Fig. 1 Preparation of cosmetics formulations for (CH, E and B) formulas

pyramid is called Top Notes, which notes the first impression: highly volatile, freshness, and sparkle. The middle layer is called the Middle or Heart Notes; it's got a body and personality. This layer is associated with fruity, spicy, and floral. The bottom layer is called Base Notes, which is known for stability (long-lasting), depth, ambery, woody, vanilla, and powdery [40, 61].

The fragrance was formulated as follows: in a dry glass beaker, the powdery raw materials (ethyl maltol, ethyl vanillin, and frambinone) were weighed and added. Then, the liquid raw materials (Aldehyde C-18, Allyl amyl glycolate, Benzyl acetate, Benzyl alcohol, Canthoxal, Citronellol, Clary Sage oil, Diethyl Phthalate, D-limonene, Eugenol pure, Galaxolide, Hedione, Hexyl cinnamic aldehyde, Hexyl Salicylate, Iso E Super, Linalool, Methyl Ionone pure, Nerol, P-cresyl methyl ether, Phenyl ethyl alcohol, Styrallyl acetate, α-Terpineol, Terpinolene, Tetrahydrogeraniol, and Dipropylene glycol (DPG)) were added. After completion of the addition, the beaker was placed on the magnetic stirrer until well mixed at room temperature. The organoleptic characteristics along with w/w percent of each raw material were presented in Table 2.

All the raw materials are subject to the International Fragrance Association (IFRA) Standards, which provide a risk management system for their safe use with the Prohibition, Restriction, and Specification [10, 15], as shown in Fig. 2.

Methodology on human subjects

Freely given, informed consent to participate was signed by all participants in the study, and a statement to the effect was declared before the study. The study was performed with the ethical approval of Ethics Committee No. 345. A total of 10 healthy adult volunteers (7 women and 3 men) between the ages of 18 and 50 were individuals with various hair types (silky, wavy, curly). Inclusion criteria are described in Table 3.

All participants are asked to use the hair conditioner normally after their daily wash of their hair (leave on hair for 10–15 min), then wash with potable water for 4 weeks, and then a complete feedback survey is collected from them.

Evaluation of formulated hair conditioners

Visual examination

The prepared formulations were inspected with homogeneity, color, and odor as described in [66].

Allergy hair test

All formulas were applied to normal human hair. The survey has been evaluated after 4 weeks of use. The test is done on human subjects under the approval of the ethical committee of the Al-Azhar University faculty of pharmacy with approval number 345; approval consent was explained and signed by each human subject before application of hair conditioner, and all the applications

Table 2 Organoleptic characteristics of each raw material

Raw Materials	Organoleptic description	W/W %	Reference
Aldehyde C18	Coconut Creamy Waxy Sweet Buttery Oily	0.5	[21]
Allyl amyl glycolate	Fruity Green Galbanum Pineapple	0.7	[16]
Benzyl acetate	Sweet Floral Fruity Jasmin Fresh	15	[57]
Benzyl alcohol	Balsamic Floral Rose Phenolic	1	[54]
Canthoxal	Anise Basil Fennel Green Raspberry Sweet	0.45	[14]
Citronellol	Bud Citrus Floral Leather Rose Waxy	7.5	[63]
Clary sage oil	Fresh Dry Herbal Sage Spicy Weedy	0.1	[24]
Diethyl phthalate	Odorless	11	[9]
D-limonene	Citrus Fresh Orange Sweet	8.5	[28]
Dipropylene glycol	Slightly alcoholic	0.8	[73]
Eugenol pure	Clove Sweet Spicy Woody	0.25	[67]
Ethyl maltol	Berry Caramellic Cotton Candy Strawberry	0.2	[76]
Ethyl vanillin	Caramel Creamy Sweet Vanilla	0.4	[56]
Frambinone	Berry Floral Raspberry Ripe Sweet	0.2	[39]
Galaxolide	Floral Musk Sweet	1.5	[23]
Hedione	Floral Green Jasmin Lactonic Tropical Natural	1.8	[77]
α-Hexyl cinnamaldehyde	Fresh Floral Green Herbal Jasmin Waxy	0.6	[31]
Hexyl salicylate	Fresh Green Herbal Orchid	1.5	[25]
Iso E Super	Ambergris Cedar Dry Ketonic Phenolic Woody	2.7	[70]
Linalool	Bois de rose Blueberry Citrus Floral Green Woody Sweet	5.8	[59]
Methyl ionone pure	Orris Violet Powdery Woody	1.6	[68]
Nerol	Citrus Floral Fruity Rose Waxy Sweet	0.69	[38]
P-cresyl methyl ether	Naphthyl Narcissus Nutty Powdery Ylang	0.01	[69]
Phenyl ethyl alcohol	Floral Fresh Honey Rose	33	[43]
Styrallyl acetate	Berry Fruity Leafy Green Musty Seedy	1.5	[8]
α-Terpineol	Citrus floral Lilac Pine Terpenic Woody	1.8	[64]
Terpinolene	fresh woody sweet pine citrus	0.25	[18]
Tetrahydrogeraniol	Aldehydic Citrus Green Leathery Musty Soapy Waxy	0.65	[20]

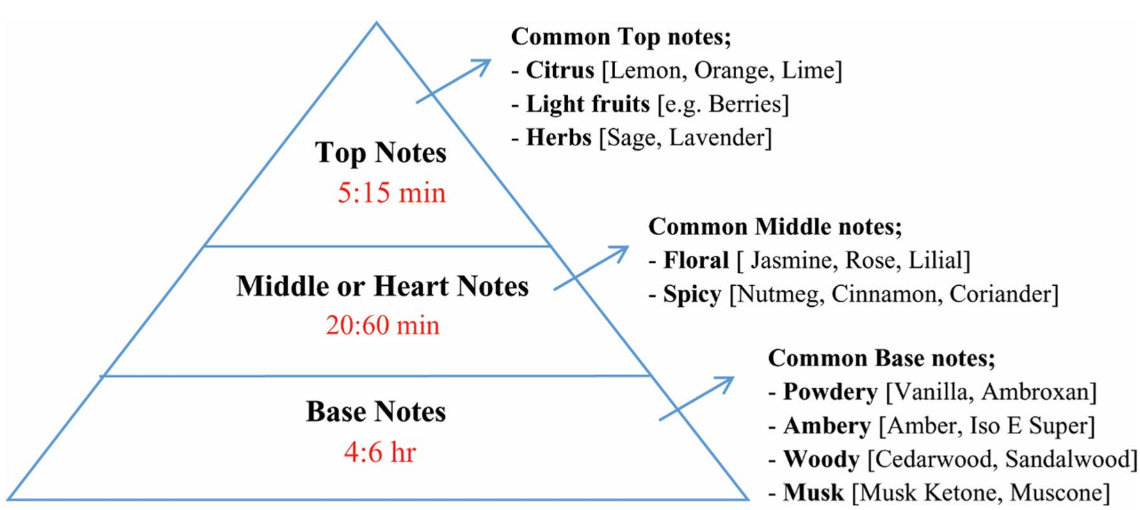


Fig. 2 The Olfactory Pyramid of Fragrances

Table 3 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Male/ female Normal hair, not colored Age 18- 50	Subjects are undergoing medical therapy for scalp, hair diseases or diabetes to ensure that the results aren't influenced by ongoing treatments. Subjects with pregnancy or breast-feeding. Hormonal changes during these periods can affect hair condition and response to products

were under medical supervision. The study aimed to evaluate hair cosmetic product consumption in subjects with a sensitive scalp [52].

Thermal stability test

The thermal stability of the formulas was tested by putting them in an incubator at 45 °C and 75% relative humidity for 3 months (90 days) [44] and checking if there were any changes in color, odor, viscosity, and pH.

Determination of pH

The pH of formulas was measured with a 10% solution in distilled water via a calibrated digital pH meter at a constant room temperature [44].

Determination of viscosity

The viscosity of the test sample was determined by the operating procedure of the viscometer with spindle 4 and rpm 12 [42].

Dirt dispersion test

A few drops of hair conditioner were added to a test tube that contained 10 ml of distilled water, followed by the addition of 1 drop of crystal violet (ink). The test tube was then sealed and well shaken. Nil, light, moderate, or heavy were the estimated levels of ink in the foam [55].

Determination of moisturizing time

A moisturizer is a type of cosmetic that works to hydrate the hair by reducing the evaporation of water from the hair. One gram of hairball was placed in the beaker, which contains 100 ml of different dilutions of conditioner, and the complete sinking time of the hairball in the conditioner was measured [13].

Determination of rinsing, combing, and the luster of hair

The action of rinsing was performed by putting 5 ml of conditioner over the hair, and then the recorded time of the hair being rinsed by water was estimated. After rinsing hair with conditioner, the action of combing was determined to check whether the comb glided smoothly or not. The luster of the hair was determined after drying the hair very well; this was estimated visually [60].

Survey evaluation methods

The survey evaluation was performed by a group of qualified experts specializing in cosmetic formulation from the faculty of pharmacy. They provided feedback using a rating scale from 5 "poor" → 10 "excellent" [36]. The number of individuals who participated in the evaluation is also noted to ensure a comprehensive assessment and they were 10 individuals. The survey was done as shown in Fig. 3.

Evaluation of formulated fragrance

Density

The density of the perfume oils was determined by the cup method at room temperature using the following Eq. (1):

$$\textbf{Density}\ (\rho) = \frac{w_1 - w_2}{v} \tag{1}$$

W_1 = Weight of oil filled on a cup (gm).
W_2 = Empty cup (gm).
V = Unit of volume (mL).

Refractive index

The refractive indices were measured on HI-96800 Digital Refractometer, HANNA Instruments, USA. The readings were taken in triplicate at room temperature.

Method of analysis

Scanning electron microscopy (SEM)

The methodology was performed at an accelerating voltage of 30 kV. The examination of all groups was done at 500 × magnification. Samples were fixed to aluminum stubs with a standard diameter using a carbon double sticky tape. A normal human hair was obtained from a local barber in the area to investigate the effect of formulated hair conditioner formulas of CH-ETD and CH-BTD on it. The obtained hair was first washed with sulfate free shampoo to ensure cleanliness and dirt-free conditions. Then the hair was divided into equal bunches or tufts of hair and fixed into a sheet for easy application of the conditioner.

The hair tufts were numbered from 1–9 by the numbers of the formulated conditioners (C1-C3 for CH containing OHC, E4-E6 for CH-ETD containing OHC, and B7-B9 for CH-BTD containing OHC), and one tuft is left as control with no application of conditioner

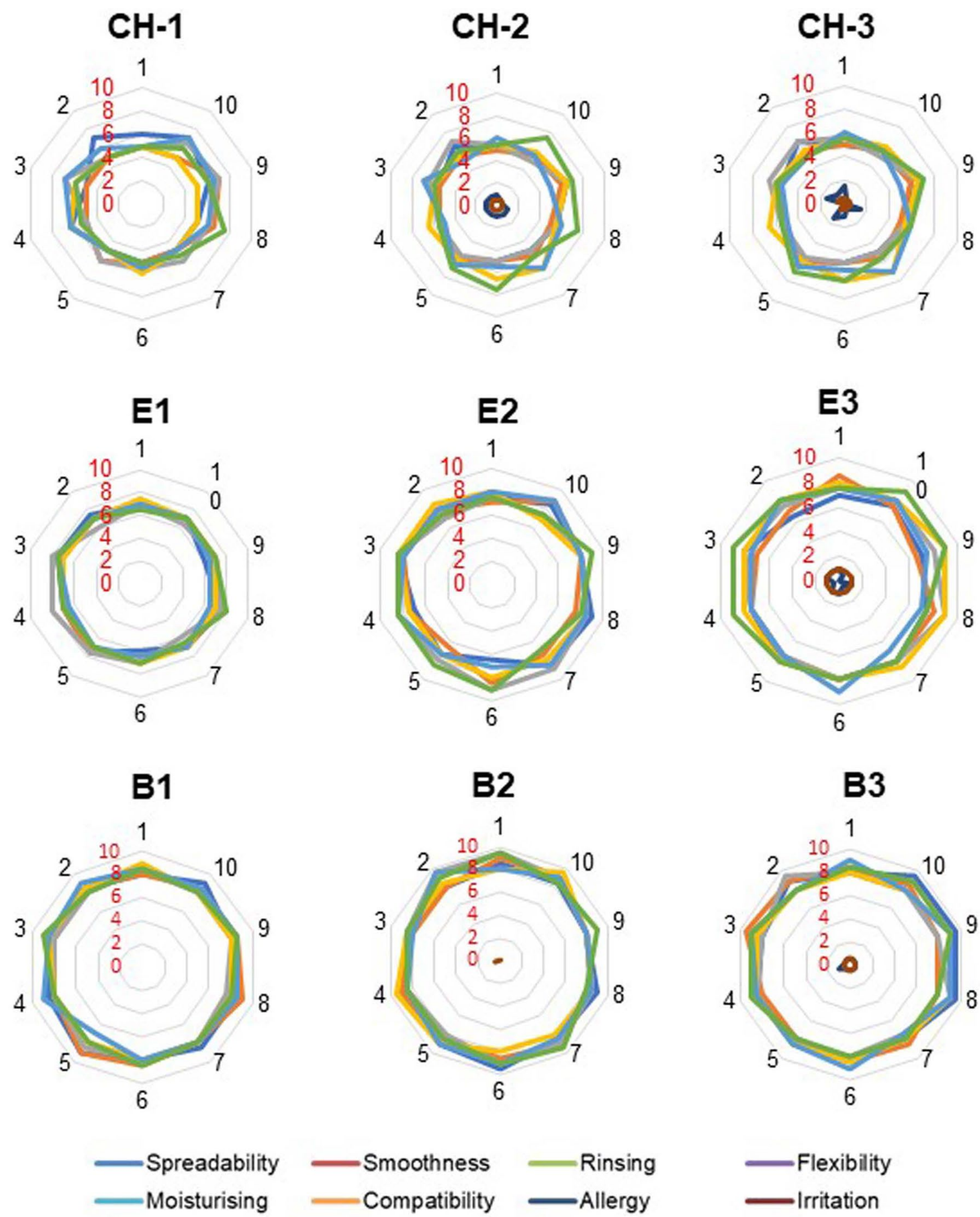


Fig. 3 Panel survey evaluation on the hair conditioner for (CH, E, and B) formulas

at all (Fig. 4). The formulated hair conditioners were applied to each tuft according to number coding on a daily basis, two times per day (once every 12 h) and left on the hair for 10 min then rinsed with pure water.

This action was continued daily for 14 days to evaluate the efficacy of the formulated hair conditioner and compare it with chitosan alone. After 14 days, the tufts were examined by an expert, and with reference to the panel

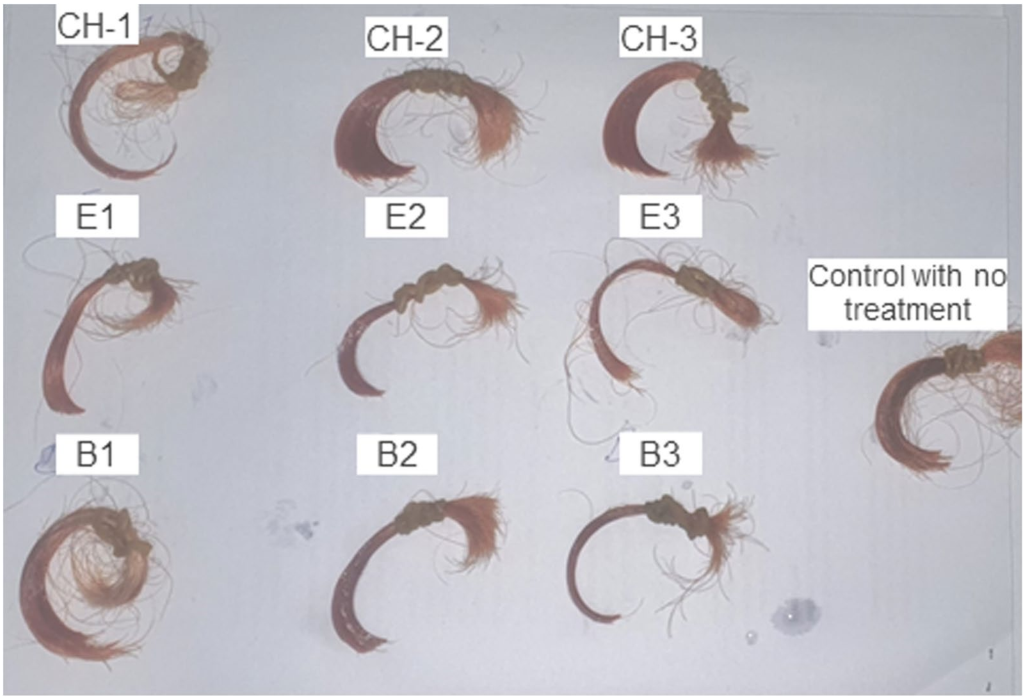


Fig. 4 Applying conditioner for (CH, E and B) formulas on normal hair

survey formulae (CH2, B2, and E2), they were examined by a scanning electron microscope with a magnification power of 100 µm and compared with control hair with no application of hair conditioner.

Molecular modeling studies

The docking simulation of CH-BTD and CH-ETD was applied against keratin using the Molecular Operating Environment program (MOE-Dock), version 2014.0901 [2, 6, 47]. The protein data bank provided the co-crystallized structure of keratin (PDB code: 4ZRY) for download [19]. The docking investigations of CH-BTD and CH-ETD were evaluated in accordance with the method mentioned in the supplementary file.

In silico ADMET prediction study

The predicted physicochemical and pharmacokinetic features of CH-BTD and CH-ETD were examined in accordance with the protocol given [3, 34, 48] employing the open-source web software SwissADME and Admet-SAR 1.0 internet server.

Results and discussions

Physical appearance

The evaluated chitosan and its derivatives were successful in that the prepared conditioners are uniform in appearance without any visible cracks or imperfections, homogenous, and there are no particles in the suspension or precipitated powder. No change in color was recorded, where all formulas showed an appearance of white to yellowish. Also, all formulas showed no volatility. The results are represented in Table 4.

Table 4 The physical characters for (CH, E, and B) formulas

Items	Color	Viscosity (Cp)	pH	Volatility	Sticky
Base	White to Yellowish	Moderate	Moderate	Non	High
CH-1	White to Yellowish	Moderate	Moderate	Non	High
CH-2	White to Yellowish	High	High	Non	Moderate
CH-3	White to Yellowish	High	High	Non	Light
E1	White to Yellowish	Moderate	Moderate	Non	High
E2	White to Yellowish	High	High	Non	Moderate
E3	White to Yellowish	High	High	Non	Light
B1	White to Yellowish	Moderate	Moderate	Non	High
B2	White to Yellowish	High	High	Non	Moderate
B3	White to Yellowish	High	High	Non	Light

Viscosity

As presented in Table 4, the viscosity of the hair conditioner base decreased after inclusion of the chitosan and chitosan derivatives into the formulas, with an exception for E1, which gave a viscosity of 26.30 ± 0.05 cP, which is slightly higher than the base (26.20 ± 0.05 cP). Among the all formulas, B3 with a viscosity of 24.00 ± 0.05 cP had the most significant reduction in viscosity. It is worth mentioning that viscosity of the hair conditioners influences factors such as ease of application, spreadability, and overall user satisfaction. A lower viscosity can enhance the product's ability to be easily dispensed and applied, which may lead to improved consumer compliance.

pH

The normal pH range for hair is slightly acidic, around 5.4–5.9 [72] and studies have found that shampoos with lower pH (≤5.5) may reduce frizz and static electricity in hair fibers [26]. For optimal hair health, a pH range of 5–7 is recommended [79].

The pH values of the nine formulas were in the normal range for hair conditioner, which is considered acceptable to avoid the risk of irritation or itching and is between 4.2 ± 0.01 and 4.9 ± 0.01. The results are represented in Table 4.

Stability and compatibility tests

The ten formulations showed stability at room temperature, refrigeration and oven during the storage period (3 months). The results are tabulated in Tables 5, 6, and 7. As presented, all OHC formulations showed no change in color, odor, and viscosity, as well as no phase separation, which indicated that the chitosan-based OHC, CH-ETD-based OHC, and CH-BTD-based OHC formulated in this study possess good stability for 90 days. The color of the formulations was assessed visually as described by [66].

Table 5 Stability test for 90 days at room temperatures for (CH, E, and B) formulas

Items	Color	Odor	Viscosity (Cp)	Homogeneity
Base	Non	Non	26,50 ± 0.05	√
CH-1	Non	Non	25,20 ± 0.05	√
CH-2	Non	Non	25,00 ± 0.05	√
CH-3	Non	Non	24,70 ± 0.05	√
E1	Non	Non	26,60 ± 0.05	√
E2	Non	Non	26,40 ± 0.05	√
E3	Non	Non	26,10 ± 0.05	√
B1	Non	Non	25,00 ± 0.05	√
B2	Non	Non	24,70 ± 0.05	√
B3	Non	Non	24,80 ± 0.05	√

* the √ sign indicates the presence of the character checked

Table 6 Stability test for 90 days at refrigeration (CH, E, and B) formulas

Items	Color	Odor	Viscosity (Cp)	Homogeneity
Base	Non	Non	26,70 ± 0.05	√
CH-1	Non	Non	25,50 ± 0.05	√
CH-2	Non	Non	25,00 ± 0.05	√
CH-3	Non	Non	24,80 ± 0.05	√
E1	Non	Non	26,90 ± 0.05	√
E2	Non	Non	26,70 ± 0.05	√
E3	Non	Non	26,40 ± 0.05	√
B1	Non	Non	25,30 ± 0.05	√
B2	Non	Non	24,90 ± 0.05	√
B3	Non	Non	24,80 ± 0.05	√

* the √ sign indicates the presence of the character checked

FT-IR compatibility study was performed; and the results were in supplementary file 2 which confirmed that the chemical structure of both CH-ETD, CH-BTD remained unchanged after being formulated into hair conditioners.

The moisturizing time

The results for moisturizing time showed that by increasing the concentration of CH-ETD and CH-BTD, the rate of moisturizing time was increased.

Dirt dispersion test

An essential factor to consider when assessing a hair conditioner's washing performance is dirt dispersion. The hair conditioner is considered poor quality if the ink was carried into the foam during the test. This indicates that the ink will re-deposit on the hair [4]. Here and as presented in Table 8, the ink was concentrated in the water component of every formula, assuring their adequate cleansing capacity and practical usefulness.

Table 7 Thermal Stability for 90 days in incubator at 45 °C for (CH, E, and B) formulas

Items	Color	Odor	Viscosity (Cp)	Homogeneity
Base	Non	Non	26,60 ± 0.05	√
CH-1	Non	Non	25,30 ± 0.05	√
CH-2	Non	Non	25,10 ± 0.05	√
CH-3	Pale brown	Non	24,70 ± 0.05	√
E1	Non	Non	26,90 ± 0.05	√
E2	Non	Non	26,50 ± 0.05	√
E3	Pale brown	Non	26,20 ± 0.05	√
B1	Non	Non	25,30 ± 0.05	√
B2	Non	Non	25,00 ± 0.05	√
B3	Pale brown	Non	24,70 ± 0.05	√

* the √ sign indicates the presence of the character checked

Table 8 Other physical evaluations for (CH, E, and B) formulas

Items	Dirt Dispersion	Ease of Rinsing	Ease of Combing	Luster of Hair	Compatibility with cosmetic base
Base	Light	Moderate	Moderate	Moderate	√
CH-1	Light	Moderate	Moderate	Moderate	√
CH-2	Light	High	High	High	√
CH-3	Light	High	High	High	√
E1	Light	Moderate	Moderate	Moderate	√
E2	Light	High	High	High	√
E3	Light	High	High	High	√
B1	Light	Moderate	Moderate	Moderate	√
B2	Light	High	High	High	√
B3	Light	High	High	High	√

* the√sign indicates the presence of the character checked

Table 9 Physico-chemical properties of the formulated fragrance

Items	Specification
Appearance	Clear Liquid
Color	Colorless to Pale-yellow
Refractive Index	1.502 @ 20 °C
Density	0.980 @ 20 °C
Solubility	Completely soluble in ethanol
Olfactive notes	Aromatic, Citrus, Jasmin, Phenolic, Sugary, Rose, Woody, and Natural herbal

Rinsing, combing, and the luster of hair

As shown in Table 8, the ease of rinsing and combing and luster of hair were improved from moderate to high by increasing the chitosan or its derivative solution from 5 ml in the formulas CH-1, E1, and B1 to 10 ml in the formulas CH-2, E2, and B2.

Evaluation of the fragrance

The fragrance made the formulas more fresh, sugary, fruity, and fixative for the hair conditioner base. The physico-chemical properties of the formulated fragrance were presented in Table 9.

Panel survey study

The panel survey study (Fig. 3) found that the (Base, CH, E, and B) formulas do not cause itching, irritation, or swilling; moreover, they can work as emollients beside their main purpose. Also, it increases hair softness and hair strength and avoids hair damage. The results of academic opinion showed that the formulas (CH-2, E2, and B2) obtained the best efficacy. So, they were picked for the upcoming evaluation process.

Extracted vivo examination of normal human hair with SEM

The main target of innovative cosmetologists is to formulate sustainable hair products with these preferred characteristics: decreasing frizz and providing a protective layer on the hair. Innovative sustainable hair products made with natural, renewable, and eco-friendly ingredients protect hair from stress conditions, low and high humidity conditions, pollution, and an increase in sebum levels [49]. The best cosmetics formulation should ensure youthful look and luster of hair by repairing the hair cuticle strength and restoring its softness, along with making the daily routine care simple. The success of the perfect hair conditioner from a cosmetologist and consumer perspective is the capability of the conditioner to protect the hair shaft by mimicking the natural hair's protective lipid layer in order to define curls, control frizz, maximize volume, and repair split ends under extreme high or low humidity conditions with just one application [17].

Chitosan and chitosan derivatives as biodegradable polymers excel at being used as carriers and, at the same time, as active pharmaceutical agents, as they have antimicrobial activity and film-forming activity. So, they provide an excellent solution for damaged hair treatment and a new approach in cosmeceutical formulations [5].

Our formulations were designed with a unique chemical composition to mimic the chemical composition of hair, which is composed of a high percent (95%) of a special protein component with a high molecular weight called keratin [49]. The keratin protein was then arranged into fibers composed of amino acids. These fibers are coiled together in a chain of α-helix structure where amino acids of keratin are bonded together by hydrogen bonds in different shapes, including dimers, protofibrils, microfibrils, and macrofibrils [62]. Another important linkage in hair structure is the S-Bond, or cystine bond, formed between cystine amino acids of the main polypeptide chain. This bond is crucial in its role in maintaining the hair's strength and resistance to abrasion. These bonds, both the hydrogen and S-bonds, are essential in cosmetic preparations.

One of the characteristic structural features of chitosan and chitosan derivatives is their characteristic polymeric polysaccharide structure, which represents an important structural component of cell walls in fungi and yeasts, as well as in the exoskeletons of insects and crustaceans. For their unique structural composition, which mimics hyaluronic acid, and because of their hydrophilic nature, the hair microfibril bundles are highly hydrated by their application and therefore useful to keep the hair soft and elastic [74, 75].

This is practically important when using chitosan and its derivatives in the formulation of conditioners, whose function is to protect the hair and preserve its softness and flexibility. As seen by SEM images of hair treated by CH-ETD and CH-BTD conditioner and compared to control and chitosan represented in Fig. 5, some damage to the keratin superficial layer appears in the image with a magnification of 100 µm where a characteristic film appears around each single hair shaft in B and E treated groups. There is also clear coverage of each single hair shaft, with the control group exhibited noticeable hair issues that were not observed in the treated groups, which showed no signs of tangling.

Groups treated by CH-BTD-based conditioner had a clear, complete film surrounding the whole single hair shaft compared to CH-ETD-based conditioner; this is due to the fact that CH-BTD has a different chemical structure and a bigger molecular weight than CH-ETD,

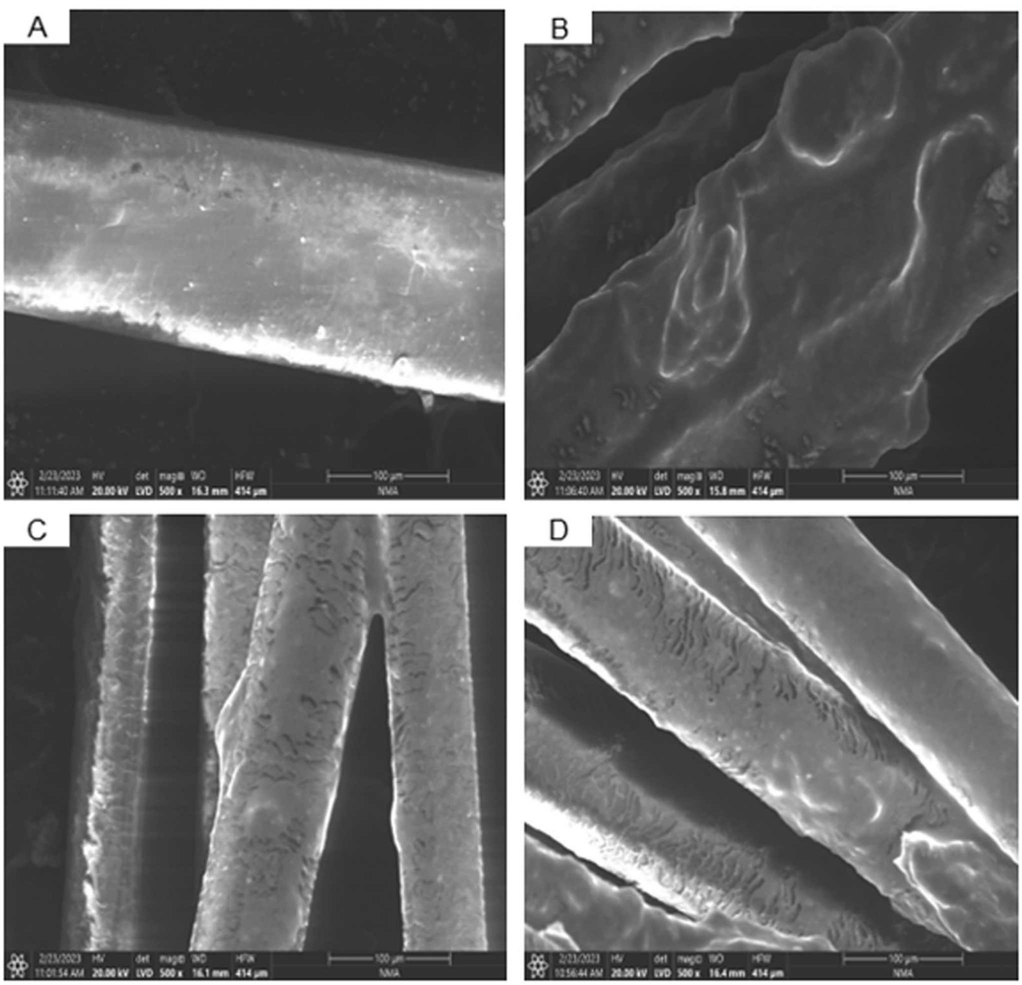
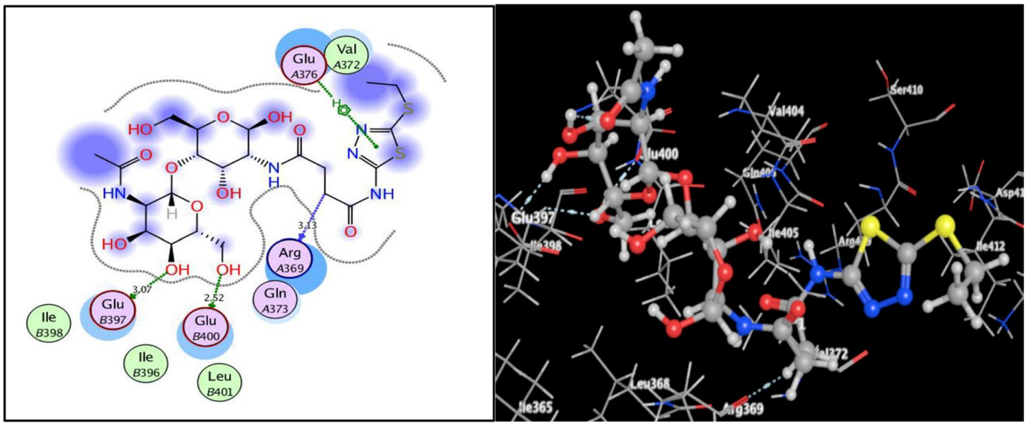
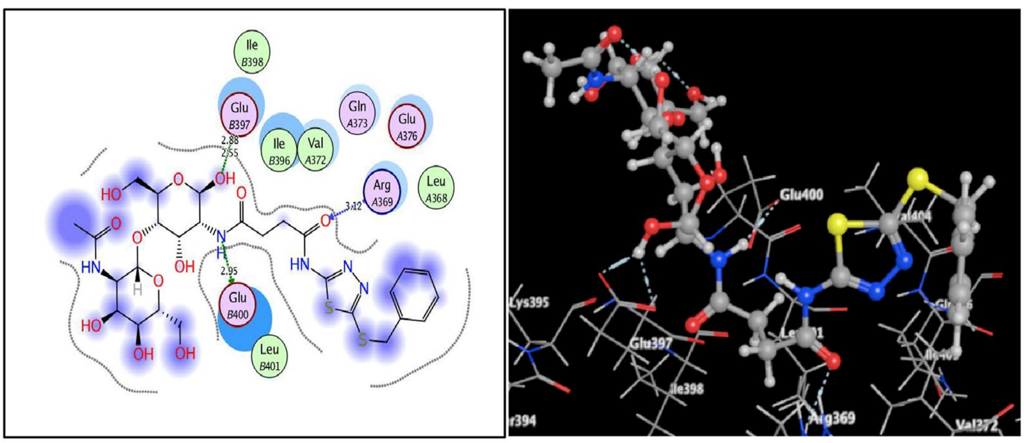


Fig. 5 Scanning Electron Microscopy Images with magnification power 100 µm of hair structure based on (CH, E, and B) formulas; Where (**A**) Normal control hair without any treatment (**B**) Normal hair treated with CH2 formula (**C**) Normal hair treated with E2 formula (**D**) Normal hair treated with B2 formula



A **B**

Fig. 6 A & B patterns clarifying the 2D and 3D binding poses of CH-ETD into active pocket of keratin, respectively (PDB code: 4ZRY)



A **B**

Fig. 7 A & B patterns clarifying the 2D and 3D binding poses of CH-BTD into active pocket of keratin, respectively (PDB code: 4ZRY)

which prevents the CH-BTD from becoming saturated in the hair follicles and enhances the formation of a clear, complete film surrounding the hair shaft. Also, it's clear from SEM images that the increase in size of the hair shaft of Band E treated groups may be attributed to the use of chitin or chitin-derived compounds, which seem able to adsorb up to 40% of their own weight in water, also retaining the right quantity of sebum internally in the keratin microfibers. Thus, the hair keratins treated by these conditioners are being more flexible in comparison with a non-treated one [1]. Therefore, the optimum formulas of CH-E/BTD were achieved from (CH-2, E2, and B2) for application as hair conditioners.

Molecular modelling

A docking simulation was performed adopting the Molecular Operating Environment (MOE-Dock) version 2014.0901 software [2, 6, 47] in order to elucidate

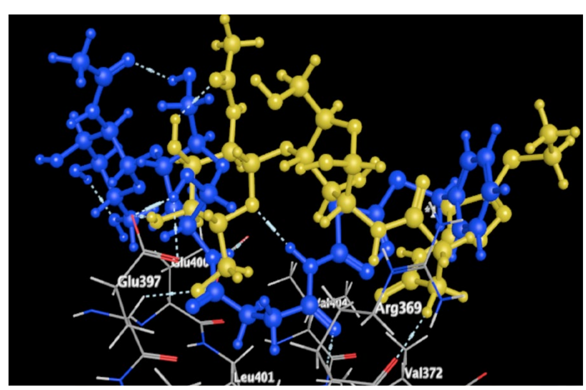


Fig. 8. 3D binding image of the superimposition between CH-ETD (yellow) and CH-BTD (blue) into active pocket of keratin (PDB code: 4ZRY)

the variations in potencies of CH-BTD and CH-ETD against keratin [19]. Figs 6, 7, 8, show the outcomes that were obtained after docking both derivatives, which gave encouraging energy scores of -10.61 and -10.82 kcal/mol, respectively.

As demonstrated in the 2D and 3D views (Figs. 6, 7), CH-BTD and CH-ETD were enclosed within the active site of keratin through hydrogen bonding with the side-chains of Glu397 and Glu400 and the backbone of Arg369. Moreover, centroid of thiadiazole moiety in CH-ETD displayed arene-H interaction with Glu376.

The superimposition (Fig. 8) confirmed the conclusion drawn from the docking investigation, which was that CH-BTD and CH-ETD occupied the same keratin active site. Furthermore, the presence of sugar moieties promotes fitting into the screening receptor's binding site by forming hydrogen bonds with the essential amino acids Glu397 and Glu400.

The physicochemical and pharmacokinetic characteristics of CH-BTD and CH-ETD, which are listed in Table 10, can be analyzed to provide essential data upon the most appropriate form of therapy. Both CH-BTD and CH-ETD were found to have good lipophilicity and water solubility as MLogP < 4.15 and −6 < Log S (ESOL) < 0. However, they provide a low expectation for their oral bioavailability (MW > 500, TPSA > 140 Å^2, number of rotatable bonds > 10, number of H-bond donors > 5, and number of hydrogen bond acceptors > 10).

Both analogues' pharmacokinetic properties demonstrated a low probability of gastrointestinal absorption and no BBB penetration. They can therefore only be applied topically and have no negative effects on the central nervous system. Table 10 illustrates that both derivatives are P-gp non-substrates, suggesting a minimal possibility of their efflux from the cell, resulting in maximum activity.

In fact, research indicates that a chemical compound may be more likely to participate in drug-drug interactions (DDI) with other active substances if it suppresses more CYP enzymes, specifically the isoforms 1A2, 3A4, 2C9, 2C19, and 2D6, that are responsible for 90% of oxidative metabolic processes [48]. Therefore, it was expected that CH-BTD and CH-ETD would fail

Table 10 Expected physicochemical and pharmacokinetic features of CH-BTD and CH-ETD

Properties	Compound	
	CH-BTD	**CH-ETD**
Physicochemical		
MW[a]	687.74	625.67
TPSA (Å^2)[b]	315.69	315.69
nRB[c]	16	15
nHBA[d]	14	14
nHBD[e]	9	9
MLogP[f]	−3.18	−3.98
ESOL[g]	−1.41	−0.29
Pharmacokinetic		
GI absorption[h]	Low	Low
BBB permeant[i]	No	No
P-gp substrate[j]	No	No
CYP1A2 inhibitor	No	No
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	No	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
hERG Inhibition[k] T_hERG_I	0.9592 (Weak inhibitor)	0.9745 (Weak inhibitor)
T_hERG_II	0.6475 (Non-inhibitor)	0.6210 (Non-inhibitor)
Carcinogens	0.8939 (Non-carcinogens)	0.8614 (Non-carcinogens)
Acute Oral Toxicity (AO)	0.5999 (III)	0.6019 (III)
Carcinogenicity (Three-class)	0.5105 (non-required)	0.5152 (non-required)

[a] Molecular Weight; [b] Topological Polar Surface Area; [c] Number of Rotatable Bond; [d] Number of Hydrogen Bond Acceptor; [e] Number of Hydrogen Bond Donor; [f] Calculated Lipophilicity (MLog Po/w); [g] Water Solubility; [h] Gastrointestinal absorption; [i] Blood brain barrier permeability; [j] p-glycoprotein substrate; [k] human Ether-a-go-related gene

to demonstrate any inhibitory effect or efficacy against these CYPs.

The human ether-a-go-go-related gene (hERG) potassium channel was not inhibited by the screening CH-BTD and CH-ETD, according to expectations. This means that there isn't a chance of cardiotoxicity or cardiac side effects, which are crucial factors to take into account while testing medication candidates in clinical trials.

Based on acute oral toxicity calculations, CH-BTD and CH-ETD derivatives yielded values of 599.9 and 601.9 $mg.kg^{-1}$, respectively. These values fall into the third category (500 $mg.kg^{-1} < LD50 \leq 5000$ $mg.kg^{-1}$), which indicates that the chemicals are safe [58]. Furthermore, the carcinogenicity descriptor (CARC) values of 510.5 and 515.2 $mg.kg^{-1}$ body weight per day suggested that these compounds could potentially fall into the non-required and non-carcinogenic categories.

Conclusion

As the cosmetic industry strives for more sustainable and naturally-derived solutions, this study's findings open a promising trajectory for innovative hair conditioner formulations that cater to both consumer preferences and performance demands. The aim of this study is to prepare a novel avenue for enhancing hair health and aesthetics by developing rinse-off hair conditioners via using the synthesized CH-E/B-TD, which were applied in a different ten formulas to examine the influence of the physicochemical properties and characterized along with the stability studies. It was found that it doesn't adversely affect the stability of the base formulations, whereas it enhances the rheological behaviors of products (CH, E, and B). The results proved that formulations had an acceptable characterization in that they were uniform in appearance, very stable without any visible cracks or changes in color or odor, and homogenous with no irritation or itching. The thermal stability thus results in an extended shelf life of 3 years.

The formulation of fragrances and their individual raw materials gave the formulas more freshness, sugary, fruity, and fixative for the base. When compared to control hair without the application of hair conditioner, each individual hair shaft in the B and E treated groups is surrounded by a distinct film under a scanning electron microscope with a magnification power of 100 µm. The control group exhibited noticeable hair issues that were not observed in the treated groups, which showed no signs of tangling, and every single hair shaft is clearly covered, where hair lacked such protective coating. Furthermore, the application of these formulations resulted in to noticeable improvements in hair condition, and tangling was significantly reduced.

The formulations of CH, E2, and B2 have showcased the most effective formulas due to their potential by imparting a protective layer that is not extremely thick and does not cause irritation, inflammation, decrease frizz, according to the end-use performance qualities. The conditioner was formulated to enhance hair health by promoting moisture retention, facilitating detangling, providing nourishment, and improving overall manageability for easier styling. The application of advanced evaluation techniques demonstrated the effectiveness of these formulations, validating their promise for addressing contemporary hair care concerns, as they are antimicrobial effective, nontoxic, environmentally compatible, and biodegradable.

Future plans

We will prioritize safety by performing toxicological studies and ensuring compliance with regulatory standards. Additionally, clinical trials will be designed to evaluate the product's efficacy across various hair types, with data collection aimed at validating its performance in terms of moisture retention, detangling, and overall hair health. These steps will collectively support a successful product launch while ensuring consumer safety and satisfaction. Future plans for the commercialization of the thiadiazole-chitosan conjugate hair conditioner include conducting a thorough market analysis to identify target consumers and establishing a strong brand identity focused on natural ingredients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13065-025-01404-6.

Additional file 1.

Additional file 2.

Acknowledgements

The authors would like to thank Faculty of Science and Faculty of Pharmacy, Al-Azhar University and Delta Aromatic International Company for supporting this research.

Author contributions

A.E. and A.D. conceptualized the study; A.E and A.D. provided the methodology; E.N. and H.D provided the software, resources and validation; A.G.I, W.E. and A.D. formally analyzed the study; A.G.I, W.E. and A.D. involved in investigation; A.E., H.D. and E.N. cured the data; A.E. and A.D. wrote the manuscript; A.G.I and W.E. reviewed and edited the manuscript; A.D., H.D. and E.N. provided the visualization, W.E. and A.G.I involved in super-vision and project administration; All authors have read and agreed to the published version of the manuscript.

Funding

This paper received no funding.

Availability of data and materials

All authors declare availability of data and materials upon request. All Data are available upon contact with Dr Ahmed Galal Ebrahim, Department of

Chemistry, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt
ahmed_polytech@azhar.edu.eg.

Declarations

Ethics approval and consent to participate
The authors declare that the test is done on human subjects in accordance with the Declaration of Helsinki under the approval of the ethical committee of the Al-Azhar University faculty of pharmacy with approval number 345; date of registration 12/8/2023. Informed consent to participate was obtained from all of the participants in the study.approval consent was explained and signed by each human subject before application of hair conditioner and all the applications were under medical supervision during the study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]MOELLHAUSEN ME FZE, Dubai, UAE. [2]Department of Chemistry, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt. [3]Department of Pharmaceutics and pharmaceutical technology, Faculty of Pharmacy (Boys), Al-Azhar University, Cairo, Egypt. [4]Department of Pharmaceutics, Faculty of Pharmacy, Sinai University-Kantara Branch, Ismailia Governorate, Egypt. [5]Department of Pharmaceutical Medicinal Chemistry and Drug Design, Faculty of Pharmacy (Girls), Al-Azhar University, Cairo 11,754, Egypt. [6]The National Committee of Drugs, Academy of Scientific Research and Technology, Cairo 11,516, Egypt. [7]Department of Pharmaceutics and pharmaceutical technology, Faculty of Pharmacy (Girls), Al-Azhar University, Cairo, Egypt.

Received: 18 July 2024 Accepted: 29 January 2025
Published online: 19 April 2025

References
1. Abd El-Hack ME, El-Saadony MT, Shafi ME, Zabermawi NM, Arif M, Batiha GE, Khafaga AF, Abd El-Hakim YM, Al-Sagheer AA. Antimicrobial and antioxidant properties of chitosan and its derivatives and their applications: a review. Int J Biol Macromol. 2020;164:2726–44.
2. Abd El-Meguid EA, El-Deen EMM, Moustafa GO, Awad HM, Nossier ES. Synthesis, anticancer evaluation and molecular docking of new benzothiazole scaffolds targeting FGFR-1. Bioorg Chem. 2022;119: 105504.
3. Alamshany ZM, Algamdi EM, Othman IM, Anwar MM, Nossier ES. New pyrazolopyridine and pyrazolothiazole-based compounds as anti-proliferative agents targeting c-Met kinase inhibition: design, synthesis, biological evaluation, and computational studies. RSC Adv. 2023;13:12889–905.
4. Alquadeib BT, Eltahir EKD, Banafa RA, Al-Hadhairi LA. Pharmaceutical evaluation of different shampoo brands in local Saudi market. Saudi Pharm J. 2018;26:98–106.
5. Amberg N, Fogarassy C. Green consumer behavior in the cosmetics market. Resources. 2019;8:137.
6. Amr AE-GE, Mageid REA, El-Naggar M, M. Naglah A, S. Nossier E & Elsayed EA,. Chiral pyridine-3, 5-bis-(L-phenylalaninyl-L-leucinyl) schiff base peptides as potential anticancer agents: design, synthesis, and molecular docking studies targeting lactate dehydrogenase-a. Molecules. 2020;25:1096.
7. Anchisi C, Meloni M, Maccioni A. Chitosan beads loaded with essential oils in cosmetic formulations. J Cosmet Sci. 2006;57:205–14.
8. Anonis DP, Perfumer CC, Forest Hills NY. Gardenia in perfumery. Gas. 1983;8:2–2.
9. Api AM. Toxicological profile of diethyl phthalate: a vehicle for fragrance and cosmetic ingredients. Food Chem Toxicol. 2001;39:97–108.
10. Api AM, Vey M. Implementation of the dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. Regul Toxicol Pharmacol. 2008;52:53–61.
11. Bakshi PS, Selvakumar D, Kadirvelu K, Kumar NS. Chitosan as an environment friendly biomaterial–a review on recent modifications and applications. Int J Biol Macromol. 2020;150:1072–83.
12. Barel AO, Paye M, Maibach HI. Handbook of cosmetic science and technology. Boca Raton: CRC Press; 2014.
13. Bazin R, Fanchon C. Equivalence of face and volar forearm for the testing of moisturizing and firming effect of cosmetics in hydration and biomechanical studies. Int J Cosmet Sci. 2006;28:453–61.
14. Beghetto V, Scrivanti A, Bertoldini M, Aversa M, Zancanaro A, Matteoli U. A practical, enantioselective synthesis of the fragrances canthoxal and silvial®, and evaluation of their olfactory activity. Synthesis. 2014. https://doi.org/10.1055/s-0034-1379254.
15. Bickers DR, Calow P, Greim HA, Hanifin JM, Rogers AE, Saurat J-H, Sipes IG, Smith RL, Tagami H. The safety assessment of fragrance materials. Regul Toxicol Pharmacol. 2003;37:218–73.
16. Boelens M, Boelens H, Boelens H. Some aspects of qualitative structure-odor relationships. Perfumer Flavorist. 2003;28:36–45.
17. Bom S, Jorge J, Ribeiro HM, Marto J. A step forward on sustainability in the cosmetics industry: a review. J Clean Prod. 2019;225:270–90.
18. Boonbumrung S, Tamura H, Mookdasanit J, Nakamoto H, Ishihara M, Yoshizawa T, Varanyanond W. Characteristic aroma components of the volatile oil of yellow keaw mango fruits determined by limited odor unit method. Food Sci Technol Res. 2001;7:200–6.
19. Bunick CG, Milstone LM. The X-ray crystal structure of the keratin 1-keratin 10 helix 2B heterodimer reveals molecular surface properties and biochemical insights into human skin disease. J Investig Dermatol. 2017;137:142–50.
20. Chen W, Viljoen AM. Geraniol—a review of a commercially important fragrance material. S Afr J Bot. 2010;76:643–51.
21. Clark GS. Ethyl methyl phenyl glycidate. Perfumer & flavorist. 1996;21:43–7.
22. Darbre PD, Harvey PW. Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. J Appl Toxicol. 2008;28:561–78.
23. David ORP. A chemical history of polycyclic musks. Chem A Eur J. 2020;26:7537–55.
24. Debnath T, Prasetyawan D & Nakamoto T. 1–3 (IEEE)
25. Di Nicolantonio L, Gigliobianco MR, Peregrina DV, Angeloni S, Ilorini L, Di Martino P, Censi R. Impact of the interactions between fragrances and cosmetic bases on the fragrance olfactory performance: a tentative to correlate SPME-GC/MS analysis with that of an experienced perfumer. Cosmetics. 2022;9:70.
26. Dias MFRG, De Almeida AM, Cecato PMR, Adriano AR, Pichler J. The shampoo pH can affect the hair: myth or reality? Int J Trichol. 2014;6:95–9.
27. El Mejri W, El Mahdi A, Mendes F, Castro R, Njim L, Zaied S, Tomás H, Baati T, Medimagh R, Khwaldia K. Chitosan films synthesized via thiol-ene click chemistry: toward safe and versatile platforms for packaging, cosmetics and biomedical applications. Sustain Chem Pharm. 2024;40: 101643.
28. Fayoux SC, Seuvre AM, Voilley AJ. Aroma transfers in and through plastic packagings: orange juice and d-limonene. A review. Part I: orange juice aroma sorption. Packag Technol Sci Int J. 1997;10:69–82.
29. Fernandez MF, Olmos B, Granada A, López-Espinosa MJ, Molina-Molina J-M, Fernandez JM, Cruz M, Olea-Serrano F, Olea N. Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: a nested case–control study. Environ Health Perspect. 2007;115:8–14.
30. Gamal A, Ibrahim AG, Eliwa EM, El-Zomrawy AH, El-Bahy SM. Synthesis and characterization of a novel benzothiazole functionalized chitosan and its use for effective adsorption of Cu (II). Int J Biol Macromol. 2021;183:1283–92.
31. Gusevskaya EV, Jiménez-Pinto J, Börner A. Hydroformylation in the realm of scents. ChemCatChem. 2014;6:382–411.
32. Guzmán E, Lucia A. Essential oils and their individual components in cosmetic products. Cosmetics. 2021;8:114.
33. Hamodin AG, Elgammal WE, Eid AM, Ibrahim AG. Synthesis, characterization, and biological evaluation of new chitosan derivative bearing diphenyl pyrazole moiety. Int J Biol Macromol. 2023;243: 125180.
34. Hashem HE, Amr AE-GE, Almehizia AA, Naglah AM, Kariuki BM, Eassa HA, Nossier ES. Nanoparticles of a pyrazolo-pyridazine derivative as potential EGFR and CDK-2 inhibitors: design, structure determination, anticancer evaluation and in silico studies. Molecules. 2023;28:7252.

35. Ibrahim AG, Hamodin AG, Fouda A, Eid AM, Elgammal WE. Fabrication and characterization of a new eco-friendly sulfonamide-chitosan derivative with enhanced antimicrobial and selective cytotoxicity properties. Sci Rep. 2024;14:10228.
36. Ishii MK. Objective and instrumental methods for evaluation of hair care product efficacy and substantiation of claims. In: Hair and hair care. England: Routledge; 2018.
37. Jayakumar R, Prabaharan M, Nair SV, Tokura S, Tamura H, Selvamurugan N. Novel carboxymethyl derivatives of chitin and chitosan materials and their biomedical applications. Prog Mater Sci. 2010;55:675–709.
38. Jirovetz L, Buchbauer G, Stoyanova A, Balinova A, Guangjiun Z, Xihan M. Solid phase microextraction/gas chromatographic and olfactory analysis of the scent and fixative properties of the essential oil of Rosa damascena L. from China. Flavour Fragr J. 2005;20:7–12.
39. Lee J. Further research on the biological activities and the safety of raspberry ketone is needed. NFS J. 2016;2:15–8.
40. Lin Z, Huang B, Ouyang L, Zheng L. synthesis of cyclic fragrances via transformations of alkenes, alkynes and enynes: strategies and recent progress. Molecules. 2022;27:3576.
41. Madera-Santana TJ, Herrera-Méndez CH, Rodríguez-Núñez JR. An overview of the chemical modifications of chitosan and their advantages. Green Materials. 2018;6:131–42.
42. Minguet M, Subirats N, Castan P, Sakai T. Behenamidopropyl dimethylamine: Unique behaviour in solution and in hair care formulations. Int J Cosmet Sci. 2010;32:246–57.
43. Mo EK, Sung CK. Phenylethyl alcohol (PEA) application slows fungal growth and maintains aroma in strawberry. Postharvest Biol Technol. 2007;45:234–9.
44. Moghimipour E, Jasemnezhad M, Mohammad Soleymani S, Salimi A. Preparation and evaluation of a free surfactant herbal shampoo with Acanthophyllum Squarrosum Saponins. J Cosmet Dermatol. 2021;20:181–7.
45. Mohamed AE, Elgammal WE, Dawaba AM, Ibrahim AG, Fouda A, Hassan SM. A novel 1,3,4-thiadiazole modified chitosan: synthesis, characterization, antimicrobial activity, and release study from film dressings. Appl Biol Chem. 2022;65:54.
46. Mohamed AE, Elgammal WE, Eid AM, Dawaba AM, Ibrahim AG, Fouda A, Hassan SM. Synthesis and characterization of new functionalized chitosan and its antimicrobial and in-vitro release behavior from topical gel. Int J Biol Macromol. 2022;207:242–53.
47. Mohi El-Deen EM, Abd El-Meguid EA, Karam EA, Nossier ES, Ahmed MF. Synthesis and biological evaluation of new pyridothienopyrimidine derivatives as antibacterial agents and escherichia coli topoisomerase II inhibitors. Antibiotics. 2020;9:695.
48. Mohi El-Deen EM, Nossier ES, Karam EA. New quinazolin-4 (3 H)-one derivatives incorporating hydrazone and pyrazole scaffolds as antimicrobial agents targeting DNA gyraze enzyme. Sci Pharm. 2022;90:52.
49. Morganti P, Morganti G, Coltelli M-B. Smart and sustainable hair products based on chitin-derived compounds. Cosmetics. 2021;8:20.
50. Mota S, Pinto C, Cravo S, Silva JR, Afonso C, Lobo JMS, Tiritan ME, Cidade H, Almeida IF. Quercus suber: a promising sustainable raw material for cosmetic application. Appl Sci. 2022;12:4604.
51. Mukherjee PK, Maity N, Nema NK, Sarkar BK. Bioactive compounds from natural resources against skin aging. Phytomedicine. 2011;19:64–73.
52. Namita N. Formulation and evaluation of herbal shampoo having antimicrobial potential. Int J Pharm Pharm Sci. 2013;5:708–12.
53. Nurani W, Anwar Y, Batubara I, Arung ET, Fatriasari W. Eucheuma cottonii as a renewable source of kappa-carrageenan and other cosmetic ingredients. Int J Biol Macromol. 2024;2:129458.
54. Paldi N, Zilber S, Shafir S. Associative olfactory learning of honeybees to differential rewards in multiple contexts—effect of odor component and mixture similarity. J Chem Ecol. 2003;29:2515–38.
55. Patil MA. Phytochemical and in-vitro evaluation of formulated polyherbal hair conditioner. J Pharmacognosy Phytochem. 2019;8:35–9.
56. Pérez-Esteve É, Lerma-García MJ, Fuentes A, Palomares C, Barat JM. Control of undeclared flavoring of cocoa powders by the determination of vanillin and ethyl vanillin by HPLC. Food Control. 2016;67:171–6.
57. Prakash O, Sahoo D, Rout PK. Liquid CO2 extraction of Jasminum grandiflorum and comparison with conventional processes. Nat Product Commun. 2012. https://doi.org/10.1177/1934578X1200700131.
58. Punarvasu T, Prashanth KH. Acute and subacute in vivo safety assessment of developed chitosan derivatives for food applications. Food Hydrocolloids Health. 2023;4: 100145.
59. Ramachanderan R, Schaefer B. Lily-of-the-valley fragrances. ChemTexts. 2019;5:1–34.
60. Reddy KV, Yachawad AV, Zambare KK, Landge S. Formulation and evaluation of herbal shampoo: Bryophyllum pinnatum. Asian J Pharmac Res. 2020;10:86–8.
61. Roberts SC, Havlicek J. Evolutionary psychology and perfume design. Appl Evolut Psychol. 2012;1:330–48.
62. Robinson VNE. A study of damaged hair. J Soc Cosmet Chem. 1976;27:155.
63. Rossiter KJ. Structure− odor relationships. Chem Rev. 1996;96:3201–40.
64. Sales A, Felipe LDO, Bicas JL. Production, properties, and applications of α-terpineol. Food Bioprocess Technol. 2020;13:1261–79.
65. Sallustio V, Rossi M, Marto J, Coelho T, Chinnici F, Mandrone M, Chiocchio I, Cappadone C, Luppi B, Bigucci F. Green extraction of Rosa canina L. and Prunus spinosa L. by NaDES and their encapsulation in chitosan nanoparticles for cosmetic industry. Ind Crops Prod. 2024;218:119042.
66. Saraf S, Hargude SM, Kaur CD, Saraf S. Formulation and evaluation of herbal shampoo containing extract of Allium sativum. Res J Top Cosmet Sci. 2011;2:18.
67. Sell C. Structure/odor correlations: the mechanism of olfaction and the design of novel fragrance ingredients. Perfumer Flavorist. 2000;25:67–73.
68. Serra S, Fuganti C, Brenna E. Synthesis, olfactory evaluation, and determination of the absolute configuration of the 3, 4-Didehydroionone Stereoisomers. Helv Chim Acta. 2006;89:1110–22.
69. Sharmeen JB, Mahomoodally FM, Zengin G, Maggi F. Essential oils as natural sources of fragrance compounds for cosmetics and cosmeceuticals. Molecules. 2021;26:666.
70. Stepanyuk A, Kirschning A. Synthetic terpenoids in the world of fragrances: Iso E Super® is the showcase. Beilstein J Org Chem. 2019;15:2590–602.
71. Suphasomboon T, Vassanadumrongdee S. Toward sustainable consumption of green cosmetics and personal care products: the role of perceived value and ethical concern. Sustain Prod Consum. 2022;33:230–43.
72. Tarun J, Susan J, Suria J, Susan VJ, Criton S. Evaluation of pH of bathing soaps and shampoos for skin and hair care. Ind J Dermatol. 2014;59:442–4.
73. Tchakalova V, Lutz E, Lamboley S, Moulin E, Benczédi D, Giuseppone N, Herrmann A. Design of stimuli-responsive dynamic covalent delivery systems for volatile compounds (part 2): fragrance-releasing cleavable surfactants in functional perfumery applications. Chem A Eur J. 2021;27:13468–76.
74. Wang L, Ezazi NZ, Liu L, Ajdary R, Xiang W, Borghei M, Santos HA, Rojas OJ. Microfibers synthesized by wet-spinning of chitin nanomaterials: mechanical, structural and cell proliferation properties. RSC Adv. 2020;10:29450–9.
75. Wang W, Xue C, Mao X. Chitosan: Structural modification, biological activity and application. Int J Biol Macromol. 2020;164:4532–46.
76. Wiedmer C, Buettner A. Identification and characterisation of odorants in a squishy toy using gas chromatography-mass spectrometry/olfactometry after thermal extraction. Anal Bioanal Chem. 2019;411:3757–61.
77. Xu L. Complex Encoding of Olfactory Information by Primary Sensory Neurons. (Columbia University, 2020).
78. Zafar N, Uzair B, Niazi MBK, Menaa F, Samin G, Khan BA, Iqbal H, Menaa B. Green synthesis of ciprofloxacin-loaded cerium oxide/chitosan nanocarrier and its activity against MRSA-induced mastitis. J Pharm Sci. 2021;110:3471–83.
79. Zamani NaN, Md Heshamuddin NS, Jafri AA, Abdullah SS & Ariff EaRE. Intelligent Manufacturing and Mechatronics: Proceedings of SympoSIMM 2020. 1171–1183 Springer. Cham

Publisher's Note