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CAFFEIC ACID ESTERS: SYNTHETIC METHODOLOGIES, ANTICANCER AND ANTI-INFLAMMATORY ACTIVITIES

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ABSTRACT: Hydroxycinnamic acids (HCA) and derivatives are well-known phenolic compounds ubiquitous in plants, showing relevant antioxidant properties as well as cytotoxicity toward several tumor cell lines. They can inhibit cell growth in a manner strongly dependent on their structural properties. Caffeic acid (CA) is one of the most widely distributed hydroxycinnamate and phenylpropanoid metabolites in plant tissues and agricultural wastes. Caffeic acid and its esters have a variety of biological activities, including antimicrobial, antioxidant, anti-inflammatory, anticancer, antiviral, anti-diabetic, anti-HIV, anti-influenza, and antimalarial activities. In most cases, the synthesis of alkyl esters can significantly improve their function. This review is an overview of the available information about the chemical synthesis, anticancer and anti-inflammatory activities of caffeic acid esters. Considering the relevance of these compounds in human health, many of them have been the focus of reviews, taking as a center their obtaining from the plants. There are few revisions that compile the chemical synthesis methods, in this way, we consider that this review does an important contribution.

INTRODUCTION: Hydroxycinnamic acids (HCA) and derivatives are well-known phenolic compounds ubiquitous in plants, showing relevant antioxidant properties as well as cytotoxicity toward several tumor cell lines. They are able to inhibit cell growth in a manner strongly dependent on their structural properties [1]. Caffeic acid 1(CA; 3,4-dihydroxycinnamic acid) **Fig. 1** is one of the most widely distributed hydroxycinnamate and phenylpropanoid metabolites in plant tissues and agricultural wastes [2]. CA, as a natural antioxidant, has received increasing attention with regard to its applications in the food, health, cosmetic and pharmaceutical industries because of its numerous biological activities, such as anti-mutagenic, anti-proliferative and anti-oxidant activities [3].

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Moreover, it has been proved in many biological investigations that caffeic acid and its analogues also display anti-inflammatory [4], antimicrobial [5], anti-HIV [6], anti-influenza [7], antidiabetic [8] and antimalarial [9] activities. However, CA exhibits low solubility and stability in various solvent systems, thus it is necessary to enhance its practical applicability by improving its solubility [10].

The strategy of esterification of hydrophilic CA with lipophilic molecules, such as aliphatic alcohols, could be employed to alter its solubility in hydrophobic media [11]. In addition, the synthesis of alkyl esters can significantly improve their function. For example, it was found that alkyl esters of CA have a higher antioxidant activity and lipophilicity than CA to protect neuronal PC12 cells against oxidative stress [12]. Therefore, it is advantageous to synthesize alkyl esters of caffeic acid based on both their biological function and potential application. There are many literature reports that address the different caffeate biological activities, much research remains to be done on this family of polyphenols, and new derivatives with

potentially higher activity than natural or synthetic products reported can be obtained. This review intends to summarize the several synthetic methods and anticancer, antioxidant and anti-inflammatory activities of these caffeic acid esters.

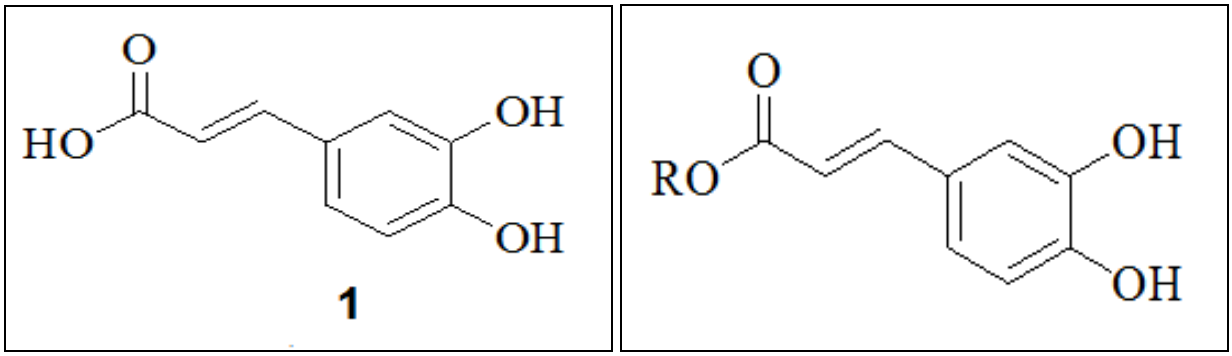
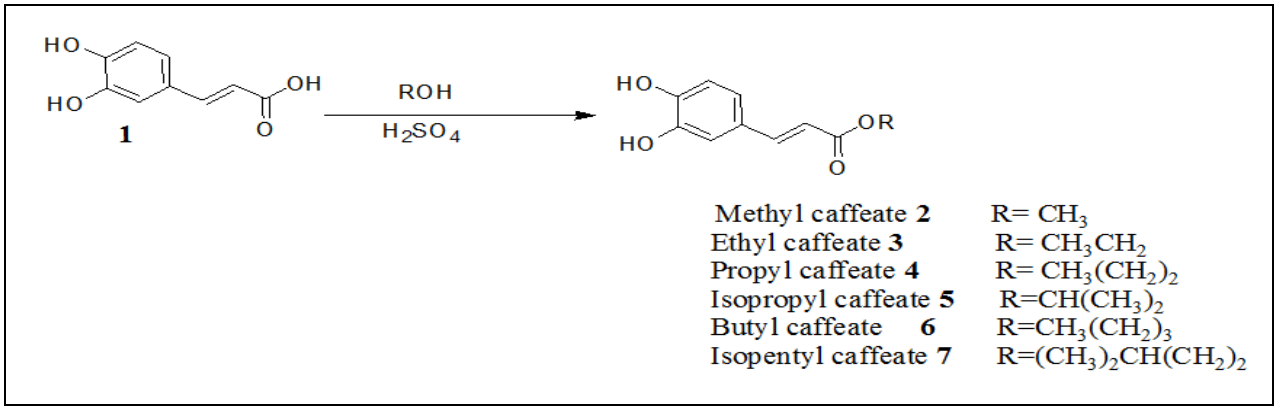


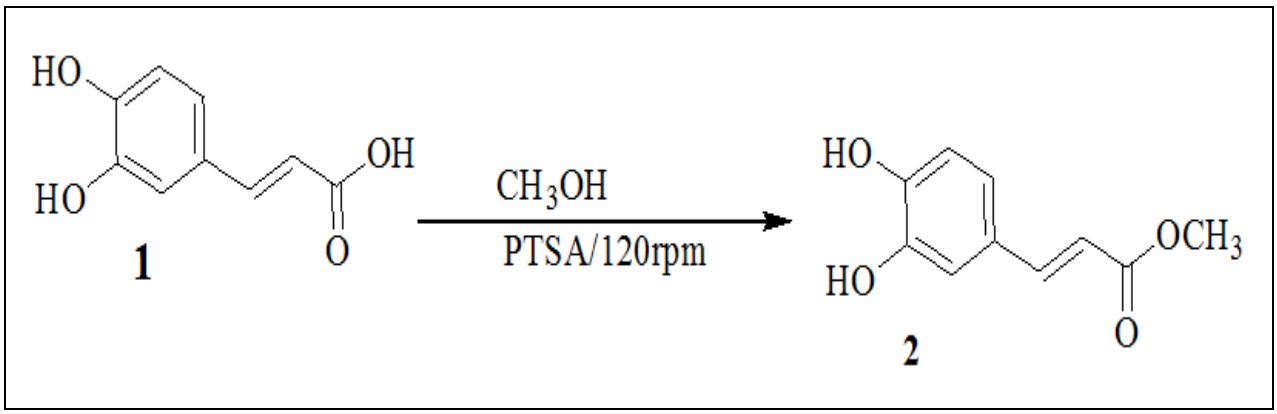
FIG. 1: CHEMICAL STRUCTURE OF CAFFEIC ACID AND CAFFEIN ACID ESTER (R= ALKYL GROUPS)

Chemical Synthesis of Caffeic Acid Esters: Caffeic acid esters may be obtained through organic synthesis methodologies from caffeic acid itself or from other chemical precursors. In different reports, caffeic acid esters have been synthesized in different methods.

Direct Esterification: Caffeic acid alkyl esters can be obtained by many different pathways. Direct esterification (Fisher method) is one of the most used synthetic strategies to obtain esters with a short alkyl chain), using in most of the cases sulfuric acid as catalyst [13-16]. Sanderson *et al.* [17] obtained caffeic acid esters (methyl caffeate 2, ethyl caffeate 3, n-propyl caffeate 4, Isoproyl caffeate 5, butyl caffeate 6, and isopentyl caffeate 7) by refluxing aliphatic alcohol, caffeic acid, and sulfuric acid, for 2 hours **Scheme 1**. Wang et al.18also synthesized methyl caffeate2using p-toluenesulfonic acid (PTSA) by the Fisher method **Scheme 2**.

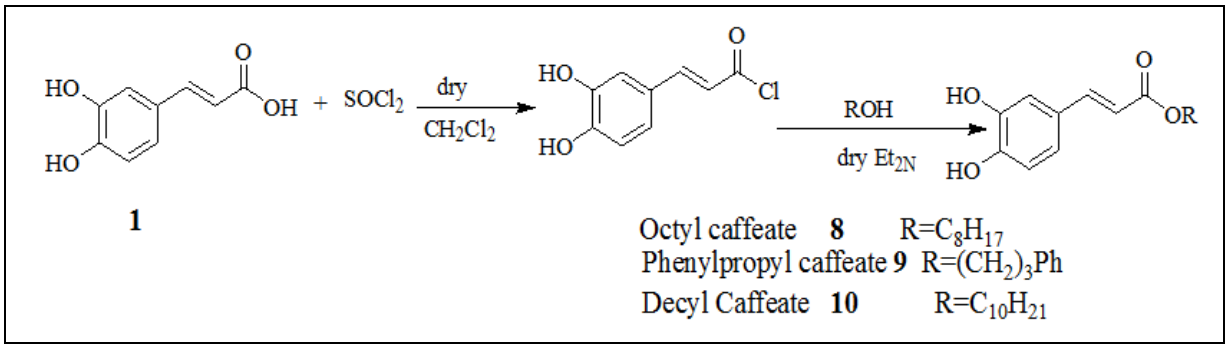


SCHEME 1: SYNTHESIS OF CAFFEIC ACID ESTERS USING H_2SO_4



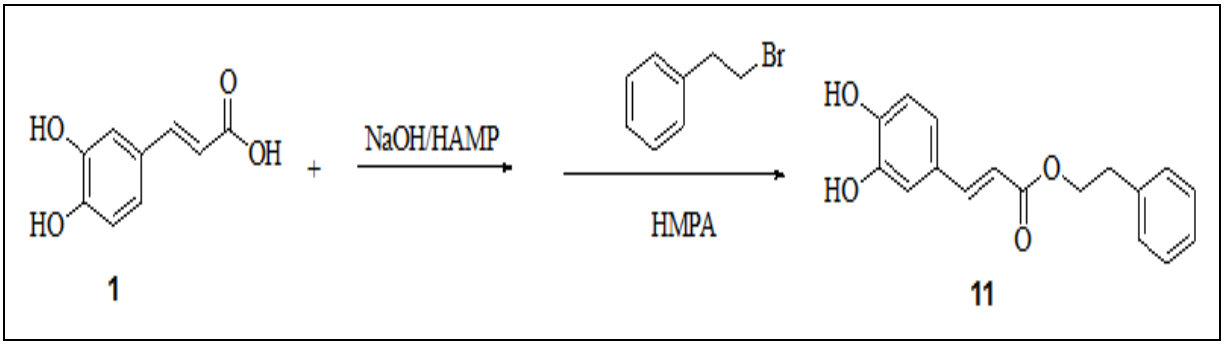
SCHEME 2: SYNTHESIS OF CAFFEIC ACID ESTERS USING PTSA

The Acyl Chloride Method: One of the most common methods reported in the literature for the synthesis of caffeic acid esters uses thionyl chloride as a reagent and transforms caffeic acid in caffeoyl chloride [19-21]. Chou *et al.*, [22] obtained caffeic acid esters from Caffeic acid and alcohols in the presence of $SOCl_2$ **Scheme 3**.



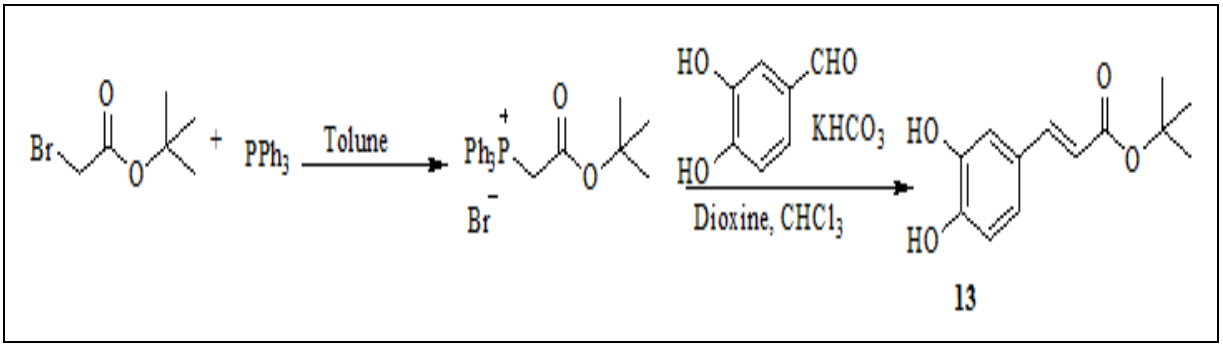
SCHEME 3: SYNTHESIS OF CAFFEIC ACID ESTERS USING ACYL HALIDE

Reaction of Caffeic Acid and Halo Hydrocarbons: Some authors synthesized alkyl caffeates by nucleophilic displacement of a halogen atom from an alkyl halide in a basic medium from caffeic acid **Scheme 4** [23].



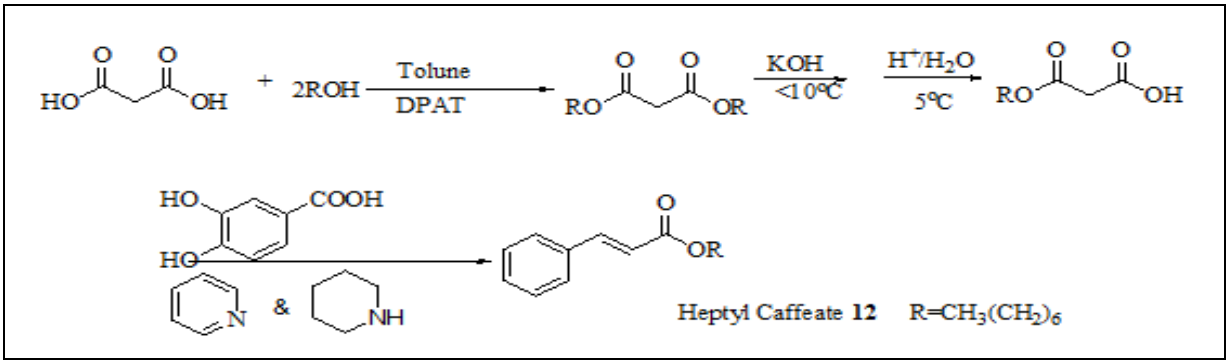
SCHEME 4: SYNTHESIS OF CAPE FROM HALOGEN SUBSTITUTED HYDROCARBON

Wittig Reaction: Wittig reaction can be used to obtain esters. The most commonly used reagents are esters of α-haloacetic acid, which, by reaction with triphenylphosphine, produce the corresponding phosphonium salt. This phosphonium salt further reacts with benzoic acid in appropriate condition produce t-butylcaffeate **Scheme 5** [23, 24].



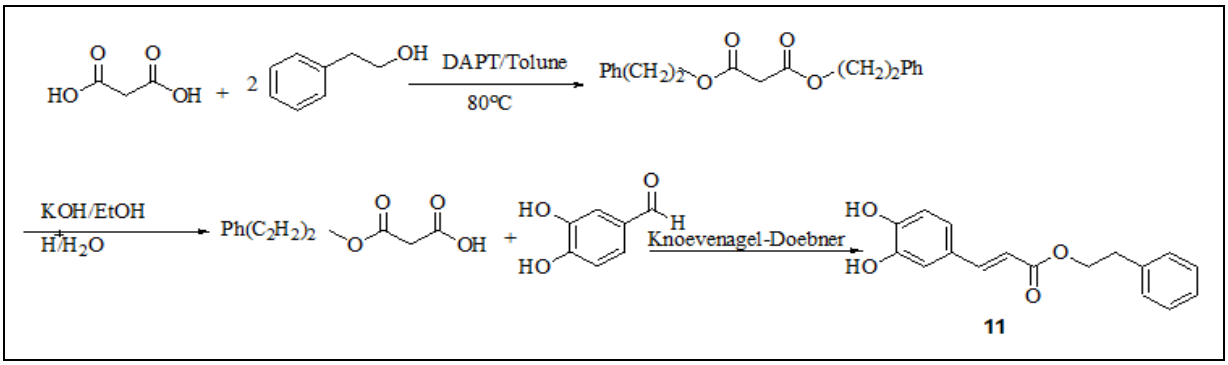
SCHEME 5: SYNTHESIS T-BUTYL CAFFEATEVIA WITTIG REACTION

Malonic Acid Monoester Method: Malonic acid monoester method is another convenient method for the synthesis of caffeic acid esters. Firstly, the malonate di-esters prepared using Wakasugi method. The malonic acid mono-esters obtained by saponification of the malonate di-esters in the presence of one equivalent of potassium hydroxide. Finally, by condensation reaction, prepared caffeic acid esters **Scheme 6** [25].



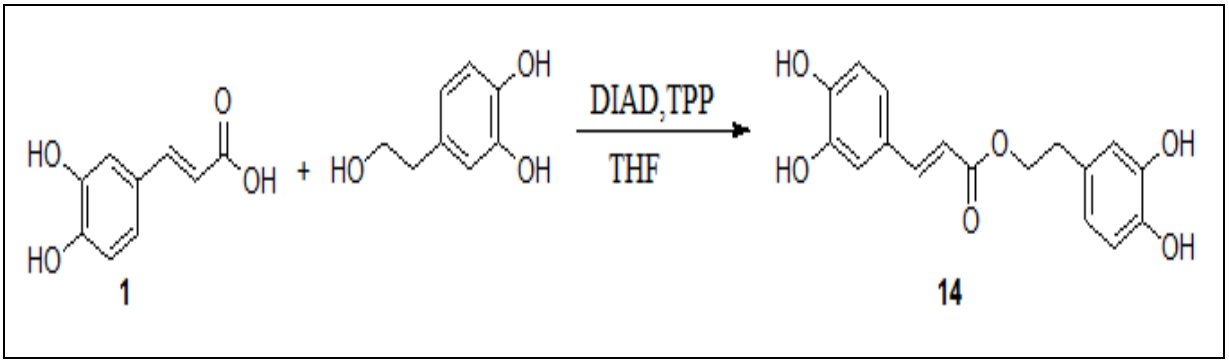
SCHEME 6: SYNTHESIS OF HEPTYL CAFFEATE FROM MALONIC ACID MONOESTER

Researchers synthesized CAPE using toluene as solvent, catalyst DPAT catalyzed malonic acid, and esterified for malonic acid diester. It reacted equimolarly with KOH for malonic acid monoester potassium single. The malonic acid monoester was obtained by acidification, then condensate for CAPE with 3,4-dihydroxy benzaldehyde by Knoevenagel-Doebner **Scheme 6** [26].



SCHEME 6: SYNTHESIS OF CAPE FROM MALONIC ACID MONOESTER

Mitsunobu Esterification of Caffeic Acid: Mitsunobu reaction is used in the synthesis of caffeic acid esters [27–29]. Chapadoet al28used this method (triphenylphosphine (TPP) and diisopropyl azodicarboxylate (DIAD) in dry tetrahydrofuran as solvent at room temperature) to obtaindihydroxyphenethyl caffeate 14 **Scheme 7**.

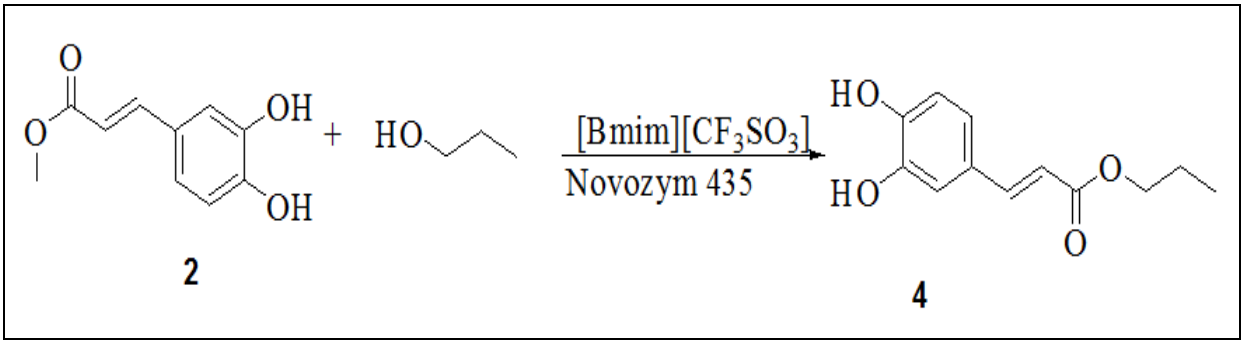


SCHEME 7: SYNTHESIS OF DIHYDROXY PHENETHYL CAFFEATE USING MITSUNOBU ESTERIFICATION

Enzymatic Synthesis of Caffeic Acid Esters: Pang *et al.* [30] was synthesized propyl caffeate using lipase-catalyzed transesterification in ionic liquid. Propyl caffeate was obtained by transesterification reaction in a 5 mL screw-capped vial at a certain temperature for 38 h with a constant stirring speed of 120 rpm. Methyl caffeate 2or ethyl caffeate3 was dissolved into 1 mL ionic liquid. The reaction was initiated by adding immobilized lipase and 1-propanol. The maximum propyl caffeate4 yield of 98.5% was obtained using lipase-catalyzed transesterification using Novozym 435 as a biocatalyst, [Bmim] [CF_3SO_3] as a medium, a molar ratio of methyl caffeate to 1-propanol of 1:5,

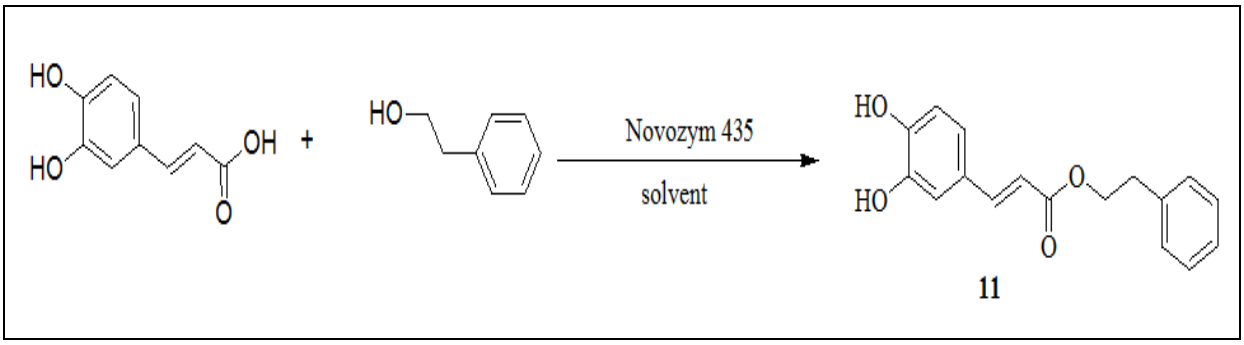
a mass ratio of methyl caffeate to lipase of 1:20, and a reaction temperature of 60 ºC. The two-step conversion of caffeic acid to propyl caffeate *via* methyl caffeate is an efficient way to prepare propyl caffeate with an overall yield of 82.7% **Scheme 8**.

Wang *et al.*, [31] improved this method in the microreactor in a short period of time (2.5 h) with a flow rate is 2 µL/min which kinetic constant, Km, was 16 times lower than that of a batch reactor.



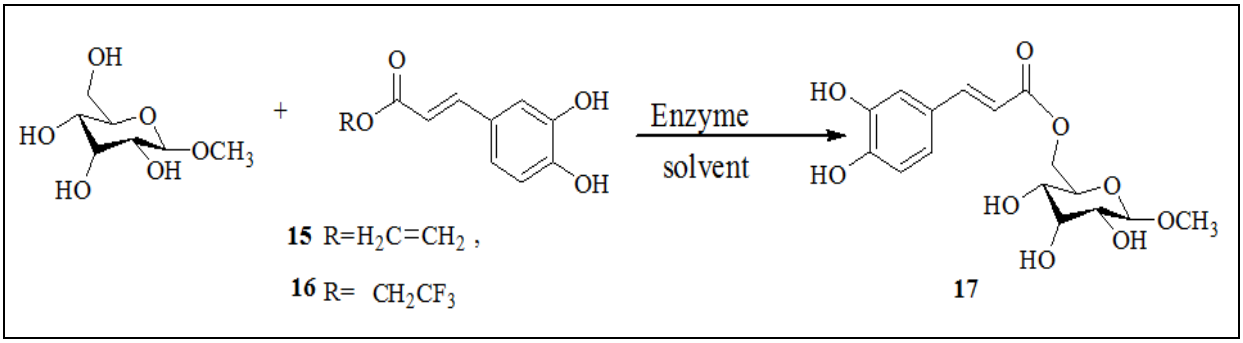
SCHEME 8: SYNTHESIS OF PROPYL CAFFEATE USING TRANSESTERIFICATION

Researchers reported candida antarctica lipase B (Novozym435) had the scope to generate CAPE by catalytic esterification of caffeic acid and phenethyl alcohol **Scheme 9** [31, 33].



SCHEME 9: SYNTHESIS OF CAPE USING NOVOZYM 435

Chyba *et. al.*, [34] reported the enzymatic caffeoylation of methyl β-D-glucopyranoside using vinyl and 2,2,2-trifluoroethyl caffeates as caffeoyl donors and lipase from thermomyces lanuginosus (Lipozyme TL IM) **Scheme 10**.



SCHEME 10: SYNTHESIS OF METHYL B-D-GLUCOPYRANOSIDE USING ENZYME

Biological Activities of Caffeic Acid Esters:

Anticancer Activity: Cancer is one of the world's major risks to human health. Epidemiological studies had shown that eating various rich vegetables, fruit, and other natural foods could significantly reduce the risk of cancer in humans [35]. CAPE was subsequently considered to be a potent anticancer component of propolis [36], and it was a natural anticancer drug with a good curative effect and with little side effect [37].

CAPE was an earlier confirmed antitumor component against general *in vivo* and *in vitro* neoplasm models, melanomas, lung and prostate cancers, and so on [38].

Research showed that CAPE in propolis had a great impact on melanoma, colorectal and gastric cancer cell lines [39]. CAPE exhibited inhibitory effects on the motility and invasion of C6 glioma cells when tested with scratch assay and Boyden chamber assay.

Furthermore, CAPE induced the expression of nerve growth factor and p75 neurotrophin receptor, which were involved in neuroal cell differentiation, inhibited the activity of MMPs, and induced the expression of RhoB, a tumor suppressor showing CAPE as an agent that possessed antitumor progression potential [40].

The effect of CAPE on cholangiocarcinoma (CCH) growth both in vitro and *in-vivo* was also studied. It decreased the growth of a number of CCH cells but not of normal cholangiocytes.

On the other hand, Bax expression was increased, whereas Bcl-2 expression was decreased in cells treated with CAPE. In BALB/c nude mice implanted subcutaneously with MzChA-1 cells treated with daily CAPE for 77 days, tumor growth was decreased, and tumor latency was increased two-fold [41].

Chiang found CAPE could significantly inhibit the growth of colorectal tumors in a mouse xenograft model. The mechanisms of action included modulation of PI3-K/Akt, AMPK, and m-TOR signaling cascades both in vitro and *in-vivo* [42].

Concerning various combined studies (both *in-vivo* and *in-vitro*), Chen found the effects of CAPE on tumor growth in relation to IL-1β signaling when examined in CE81T (human esophageal cancer cells) and CCL-241 cells (human normal intestine cell line) [43].

The effects of CAPE in a breast cancer model, including tumor growth both *in-vitro* and *in-vivo*, were examined, and its effects on the cell cycle, apoptosis, and angiogenesis in the hormone receptor-negative MDA-231 and hormone receptor-positive MCF-7 breast cancer cell lines were analyzed [44]. Sanderson *et al.*, [17] synthesized and evaluated the effects of caffeic acid1, CAPE 11, and synthetic alkyl caffeic acid esters (methyl caffeate 2, Ethyl caffeate 3, propyl caffeate 4, isopropyl caffeate 5, n-butyl caffeate 6, isopentyl caffeate 7) **Table 1** on cell viability and androgen-dependent cell proliferation, subcellular localization and expression of androgen receptor (AR) and secretion of prostate-specific antigen (PSA) in LNCaP human hormone-dependent prostate cancer cells.

Fiuza *et al.*, [14] also tested caffeic acid esters (methyl caffeate 2, propyl caffeate 4, octyl caffeate, 8), in a human cervix adenocarcinoma cell line-HeLa (epithelial-like adherent line).

In order to determine the degree of toxicity of these compounds towards healthy cells, experiments were also carried out in non-neoplastic cells-fibroblasts from human embryonic lung tissue (L-132).

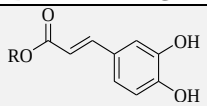
Nagaoka *et al.*, [45] synthesized caffeic acid esters and were tested for their anti-proliferative activities toward six different tumor celllines, that is, murine colon 26-L5 carcinoma (colon 26-L5), murine B16-BL6 malonoma (B16-BL6), murine Lewis lung carcinoma (LLC), human HT-1080 fibrosarcoma (HT-1080), human lung A549 adenocarcinoma (A549), and human cervix HeLa adenocarcinoma (HeLa) cell lines. The anti-proliferative activities of 11,18–26 and 22-29are summarized in terms of their EC_{50} values in **Table 1**.

All these esters showed stronger anti-proliferative activity than caffeic acid, and all the compounds except for20 and 21 showed the strongest activity toward colon26-L5 cell line.

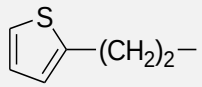
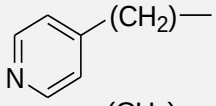
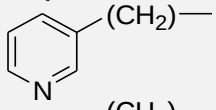
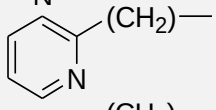
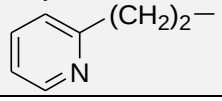
Interestingly, the CAPE analogues revealed no cytotoxic effect toward primary cultured mouse hepatocytes up to 100 mM concentration.

This indicates that CAPE and its analogues possessed selective anti-proliferative activity toward colon 26-L5 cellline. Especially, the activities of compounds 20 and 26 (EC50: 0.02 and 0.02μM, respectively) were stronger than those of 5-fluorouracil (EC50:0.06 μM) and doxorubicin (EC50: 0.04 μM), which were used as positive controls.

TABLE 1: CYTOTOXIC AND ANTI-PROLIFERATIVE ACTIVITIES OF CAFFEIC ACID AND CAFFEIC ACID ESTERS AGAINST DIFFERENT CANCER CELL LINES.

	 Compounds	R	Cell line	Cytoxicity activity (IC50 µM	Ref.	Anti-proliferative activities (IC_{50} µM)	Refs.
	Caffeic acid	H	LNCaP	>100	[17]		
1						-	-
			A549	-	-	288	[45]
			HeLa	-	-	300	[45]
			Colon 26-L5	-	-	43.6	[45]
			LLC	-	-	318	[45]
11	CAPE	$–(CH_2)_2Ph$	B16 BL-6	-	-	314	[45]
			HT-1080	-	-	257	[45]
			HeLa	12.3	[29]	10.7	[45]
			SK-OV-3	42.1	[29]	-	-
			HT-29	25.1	[29]	-	-
			LNCaP	33.7	[17]	-	-
			Colon 26-L5	-	-	0.15	[45]
			LLC	-	-	2.57	[45]
			B16-BL-6	-	-	2.18	[45]
			HT-1080	-	-	14.4	[45]
			A549	-	-	32.4	[45]
18	Benzyl caffeate	$–CH_2Ph$	Colon 26-6	-	-	1.34	[45]
			LLC	-	-	5.73	[45]
			B16-BL-6	-	-	7.90	[45]
			HT-1080	-	-	12.1	[45]
			A549	-	-	19.6	[45]
			HeLa	-	-	25.3	[45]
	3-Phenyl-propyl Caffeate	$–(CH_2)_3Ph$	Colon 26-6	-	-		
19			LLC	-	-	22.0	[45]
			B16 -BL-6	-	-	2.32	[45]
			HT-1080	-	-	2.16	[45]
			A549	-	-	18.1	[45]
			HeLa	-	-	23.5	[45]
						22.0	[45]
20	4-Phenylbutyl caffeate	$–(CH_2)_4Ph$	Colon 26-6	-	-	0.02	[45]
			LLC	-	-	2.29	[45]
			B16 -BL-6	-	-	1.99	[45]
			HT-1080	-	-	13.3	[45]
			A549	-	-	31.6	[45]
			HeLa	-	-	20.0	[45]
21	5-Phenylpentyl caffeate	$–(CH_2)_5Ph$	Colon 26-L6	-	-	0.08	[45]
			LLC	-	-	1.27	[45]
			B16 -BL-6	-	-	2.12	[45]
			HT-1080	-	-	7.38	[45]
			A549	-	-	21.9	[45]
			HeLa	-	-	10.6	[45]
22	6-Phenylhexyl caffeate	$–(CH_2)_6Ph$	Colon 26-L6	-	-	0.08	[45]
			LLC	-	-	1.40	[45]
			B16 -BL-6	-	-	1.85	[45]
			HT-1080	-	-	10.4	[45]
			A549	-	-	21.4	[45]
			HeLa	-	-	9.11	[45]
23	8-Phenyloctyl caffeate	$–(CH_2)_8Ph$	Colon 26-L6	-	-	0.09	[45]
			LLC	-	-	0.84	[45]
			B16 -BL-6	-	-	1.81	[45]
			HT-1080	-	-	20.2	[45]
			A549	-	-	22.4	[45]
			HeLa	-	-	2.61	[45]

24	12-Phenyldodecanylcaffeate	$–(CH_2)_{12}Ph$	Colon 26-L6	-	-	1.75	[45]
			LLC	-	-	8.11	[45]
			B16 -BL-6	-	-	17.2	[45]
			HT-1080	-	-	62.8	[45]
			A549	-	-	21.2	[45]
			HeLa	-	-	18.4	[45]
25	Cinnamyl caffeate	$CH_2CH=CHPh$	Colon 26-L6	-	-	0.22	[45]
			LLC	-	-	2.16	[45]
			B16 -BL-6	-	-	2.83	[45]
			HT-1080	-	-	17.1	[45]
			A549	-	-	50.0	[45]
			HeLa	-	-	11.5	[45]
26	Phenyl-7-octenyl caffeate	$–(CH_2)_6CH=CHPh$	Colon 26-L6	-	-	0.02	[45]
			LLC	-	-	0.88	[45]
			B16 -BL-6	-	-	1.77	[45]
			HT-1080	-	-	10.51	[45]
			A549	-	-	22.3	[45]
			HeLa	-	-	1.93	[45]
2	Methyl Caffeate	CH_3	LNCaP	>100	[17]	-	-
			Colon 26-L6	-	-	3.27	[45]
			LLC	-	-	4.61	[45]
			B16-BL-6	-	-	16.7	[45]
			HT-1080	-	-	35.2	[45]
			A549	-	-	43.7	[45]
			HeLa	-	-	26.8	[45]
3	Ethyl Caffeate	$–CH_2CH_3$	LNCaP	>100	[17]	-	-
			Colon 26-L6	-	-	1.14	[45]
			LLC	-	-	4.39	[45]
			B16 -BL-6	-	-	4.64	[45]
			HT-1080	-	-	33.4	[45]
			A549	-	-	61.9	[45]
			HeLa	-	-	24.4	[45]
4	n-Propyl caffeate	$–(CH_2)_2CH_3$	LNCaP	60.7	[17]	-	-
			HeLa	12.0	[14]	21.9	[45]
			Colon 26-L6	-	-	1.52	[45]
			LLC	-	-	3.30	[45]
			B16 -BL-6	-	-	3.87	[45]
			HT-1080	-	-	17.9	[45]
			A549	-	-	42.9	[45]
			L-132	9.0	[14]	-	
5	I-propyl caffeate	$–CH(CH_3)_2$	LNCaP	51.9	[17]	-	-
6	n-Butyl caffeate	$–(CH_2)_3CH_3$	LNCaP	45.4	[17]	-	-
			Colon 26-L6	-	-	0.27	[45]
			LLC	-	-	2.48	[45]
			B16 -BL-6	-	-	2.78	[45]
			HT-1080	-	-	20.2 4	[45]
			A549	-	-	2.2	[45]
			HeLa	-	-	4.02	[45]
7	Isopentyl caffeate	$– (CH_2)_2CH(CH_3)_2$	LNCaP	45.4	[17]	-	-
8	n-Octyl caffeate	$–(CH_2)_7CH_3$	HeLa	-	-	2.40	[45]
			Colon 26-L6	70.0	[14]	0.22	[45]
			LLC	-	-	1.19	[45]
			B16 -BL-6	-	-	2.23	[45]
			HT-1080	-	-	20.0	[45]
			A549	-	-	34.6	[45]
			L-132	22.0	[14]	-	-
10	n-Decyl caffeate	$–(CH_2)_9CH_3$	Colon 26-L6	-	-	0.25	[45]

			LLC	-	-	1.15	[45]
			B16 -BL-6	-	-	2.06	[45]
			HT-1080	-	-	14.2	[45]
			A549	-	-	21.4	[45]
			HeLa	-	-	1.85	[45]
27	n-Dodecyl caffeate	$-(CH_2)_{11}CH_3$	Colon 26-L6	-	-	0.29	[45]
			LLC	-	-	0.77	[45]
			B16 -BL-6	-	-	1.80	[45]
			HT-1080	-	-	19.1	[45]
			A549	-	-	21.4	[45]
			HeLa	-	-	2.00	[45]
28	n-Tetradecyl caffeate	$-(CH_2)_{13}CH_3$	Colon 26-6	-	-	16.1	[45]
			LLC	-	-	2.56	[45]
			B16 -BL-6	-	-	14.7	[45]
			HT-1080	-	-	19.9	[45]
			A549	-	-	18.5	[45]
			HeLa	-	-	10.0	[45]
29	n-Hexadecanyl caffeate	$-(CH_2)_{15}CH_3$	Colon 26-6	-	-	10.2	[45]
			LLC	-	-	13.3	[45]
			B16 -BL-6	-	-	15.6	[45]
			HT-1080	-	-	36.9	[45]
			A549	-	-	23.7	[45]
			HeLa	-	-	14.6	[45]
30	(E)-2-(thiophen-2-yl) ethyl 3(3,4dihydroxyphenyl) acrylate		HeHa	17.4	[29]	-	-
			SK-OV-3	73.2	[29]	-	-
			HT-29	37.4	[29]	-	-
31	(E)-pyridin-4-ylmethyl 3-(3, 4-dihydroxyphenyl) acrylate		HeHa	143.7	[29]	-	-
			SK-OV-3	121.7	[29]	-	-
			HT-29	187	[29]	-	-
32	((E)-pyridin-3-yl methyl 3-(3,4dihydroxyphenyl) acrylate		HeHa	82.7	[29]	-	-
			SK-OV-3	121.7	[29]	-	-
			HT-29	127.1	[29]	-	-
33	(E)-pyridin-2-ylmethyl 3(3,4dihydroxyphenyl) Acrylate		HeHa	121	[29]	-	-
			SK-OV-3	147	[29]	-	-
			HT-29	57.3	[29]	-	-
34	(E)-2-(pyridin-2-yl) ethyl 3-(3,4-dihydroxyphenyl) acrylate		HeHa	37.2	[29]	-	-
			SK-OV-3	54.1	[29]	-	-
			HT-29	43.2	[29]	-	-

Heterocyclic esters of caffeic acid were synthesized using Mitsunobu reaction. Those heterocyclic esters of caffeic acid [30-34] **Table 1** were evaluated for their cytotoxic activity against HeLa, SK-OV-3, and HT-29 cancer cell lines. All compounds had good inhibitory activity (IC_{50} = 10-200 μM) against HeLa and HT-29 but they did not show significant inhibitory activity (IC_{50} > 100 μM) against SK-OV-3 [29].

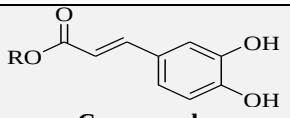
Anti-Inflammatory Activities: Caffeic acid has been shown to possess anti-inflammatory properties, since it inhibits 5- and 12 lipoxygenase activities, 46 in addition to inhibiting PKC, PKA and NF-kB activation induced by ceramides in U937 cells [47]. These anti-inflammatory actions extend to some of the caffeic acid derivatives.

Caffeic acid phenetyl ester (CAPE), a caffeic acid derivative originally isolated from the honeybee propolis, is able to specifically and potently inhibit NF-kB [48, 49]. Furthermore, CAPE is effective in suppressing 5-LOX activity, [50] as well as TPA-induced PGE2 production in human oral epithelial cells [51]. Incubation of RAW macrophages with this caffeic acid derivative inhibits LPS-induced iNOS expression [52]. Finally, in a rat model of vascular injury, the administration of CAPE diminishes COX-2 expression, NF-kB activation, and restenosis [53].

Da Cunha *et al.*, [54] studied in vitro and in vivo effects of five caffeic acid derivatives (caffeic acid, methyl, ethyl, butyl, octyl and benzyl esters) and compared their actions to those of CAPE. In the

model of LPS-induced nitric oxide (NO) production in RAW 264.7 macrophages, the pre-incubation of all derivatives inhibited nitrite accumulation on the supernatant of stimulated cells, with mean IC50 (μM) values of 21.0, 12.0, 8.4, 2.4, 10.7 and 4.80 for methyl caffeate 2, ethyl caffeate 3, butyl caffeate 6, octyl caffeate 9, benzyl caffeate18and CAPE11, respectively (Table-3). The effects of caffeic acid derivatives seem to be related to the scavenging of NO, as the compounds prevented SNAP-derived nitrite accumulation and decreased iNOS expression. Uwai *et al.*, [19] examined the function of the ester functional group and the alkyl side chain (alcoholic part) and transformed caffeic acid to several derivatives. The inhibitory effect of these derivatives on NO production in murine macrophage RAW264. When the alkyl chain was C0–C11, the EC50 values of the caffeic acid esters decreased with the increasing length of the alkyl chain. In contrast, for esters with C6–C18 alkyl chains, their EC_{50} values were almost constant. Undecyl 57 and dodecyl 27 caffeate were most potent cytotoxic compounds **Table 2**. Isopropyl ester 5, with the same alkyl chain length as ethyl ester 3 and the same carbon number as propyl ester 4, showed a similar EC_{50} value to propyl ester 4. A similar result was obtained in the case of Cyclohexyl [40] and benzyl [18] esters showed low cytotoxicity. These results suggested that the balance between lipophilicity and the size of the alcoholic moieties affected the cytotoxicity levels. However, prenyl [41], geranyl [42], and farnesyl [43] esters, which were anticipated to be lipophilic and cell membrane-philic relative to their corresponding straight chain esters, showed EC50 values 2 to 6 times higher than butyl 6, octyl 8, and dodecyl 27 caffeates, respectively.

TABLE 2: TOXICITY AND NO INHIBITION OF THE CAFFEIC ACID AND CAFFEIC ACID ESTERS



Compounds		R	Toxicity (IC_{50}μM)	NO Inhibition (IC_{50}μM)	Refs.
1	Caffeic acid	H	3406.000	165.295	[15]
2	Methyl caffeate	CH_3	367.500	3.199	[19]
				21.4	[54]
3	Ethyl caffeate	C_2H_5	121.700	3.183	[19]
				11.9	[50]
4	Propyl caffeate	C_3H_7	26.420	0.440	[19]
6	Butyl caffeate	C_4H_9	7.419	0.240	[19]
			-	8.4	[54]
35	Hexyl caffeate	C_6H_{12}	2.677	0.340	[19]
36	Heptyl caffeate	C_7H_{15}	4.594	0.236	[19]
8	Octyl caffeate	C_8H_{17}	1.588	0.060	[19]
			-	2.4	[54]
37	Nonyl caffeate	C_9H_{19}	1.658	0.052	[19]
10	Decyl caffeate	$C_{10}H_{21}$	1.542	0.045	[19]
37	Undecyl caffeate	$C_{11}H_{23}$	1.188	0.018	[19]
26	Dodecyl caffeate	$C_{12}H_{25}$	1.000	0.556	[19]
27	n-tetradecyl caffeate)	$C_{14}H_{29}$	1.256	0.292	[19]
28	n-hexadecyl caffeate	$C_{16}H_{33}$	3.200	0.713	[19]
38	n-octadecyl caffeate	$C_{18}H_{37}$	2.671	0.573	[19]
5	isopropyl caffeate	$(CH_3)_2CH$	42.200	0.302	[19]
39	sec-butyl caffeate	$C_2H_3(CH_3)_2$	13.000	0.303	[19]
40	Cyclohexyl caffeate	Cyclo-Hexyl	28.700	1.655	[19]
18	Benzyl caffeate	Benzyl	38.800	0.347	[19]
				10.7	[54]
41	Prenyl caffeate	Prenyl	30.000	0.578	[19]
42	Geranyl caffeate	Geranyl	3.054	0.223	[19]
43	Farnesyl caffeate	Farnesyl	2.658	0.258	[19]
11	CAPE	Phenethyl	4.518	0.193	[19]
				4.8	[52]

CONCLUSION: In addition to extraction from natural sources, there are cheap and easy to make synthetic methods for obtaining caffeic acid esters. These methods, unlike the extractive ones, could

provide enough quantity of caffeic acid derivatives for their multiple uses, besides guaranteeing the preservation of the plants as a natural resource. In this review, the alternatives for the synthetic obtaining of esters of caffeic acid by simple synthetic methods and their anticancer and anti-inflammatory activities are shown.

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