14° CONGRESSO NAZIONALE SINut

SINut Società Italiana di Nutraceutica

12-14 settembre 2024

Bologna

Nutraceutica himalaiana

Prof. Nicola Ferri

Dipartimento di Medicina

Università degli Studi di Padova

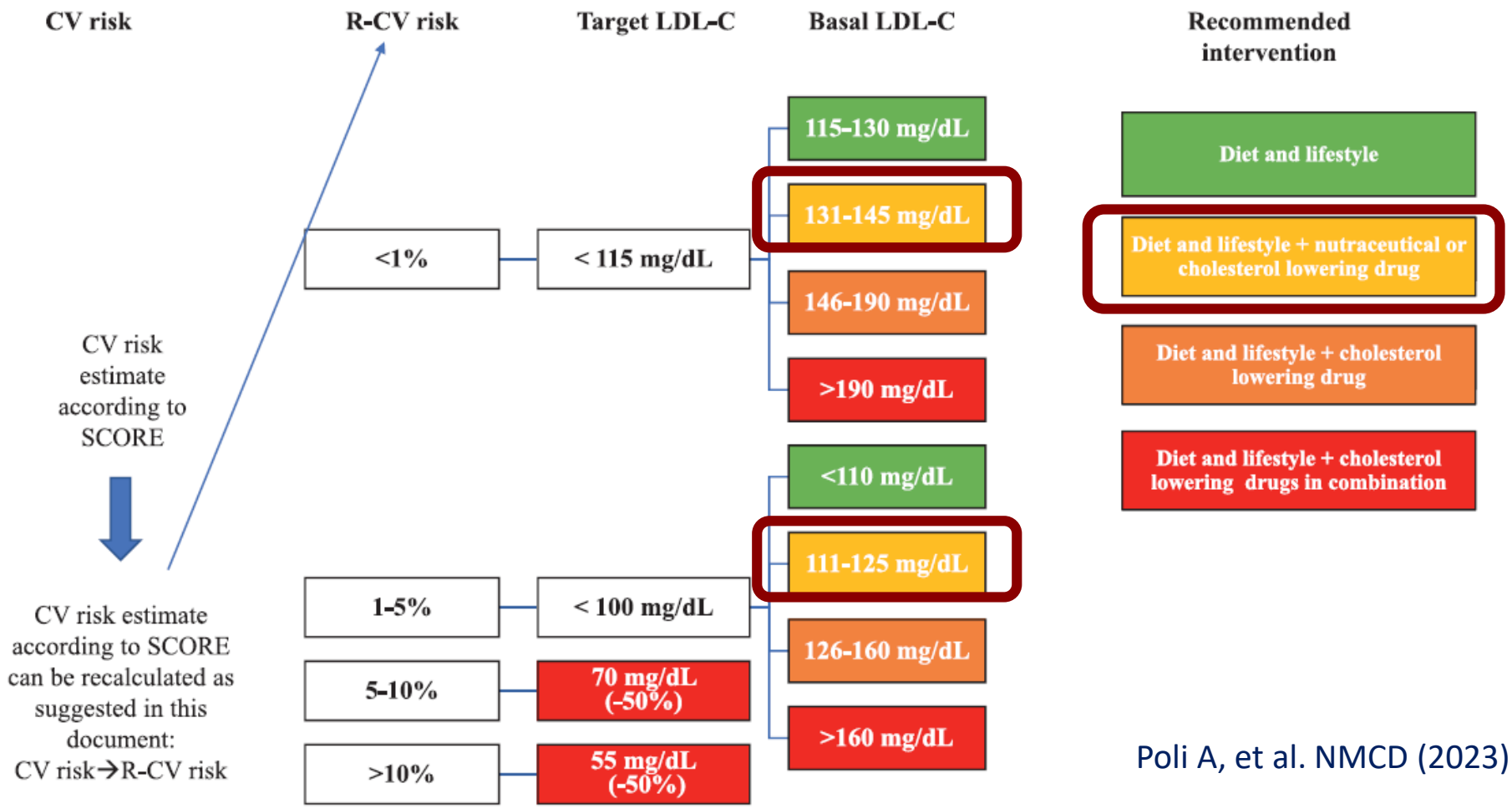
Il sottoscritto Nicola Ferri
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *Daiichi-Sankyo*
- *Pfizer*
- *Pharmanutra*
- *Relmada Therapeutics*
- *Recordati*

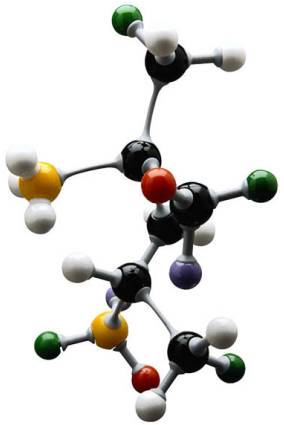
Suggested treatment flowchart for subjects in primary prevention >40 years of age



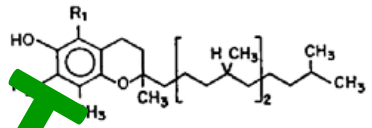
Poli A, et al. NMCD (2023) 33, 245e257

The arsenal!

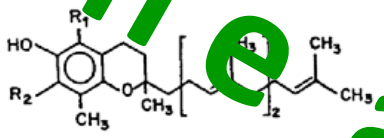
Octacosanol



Tocopherol



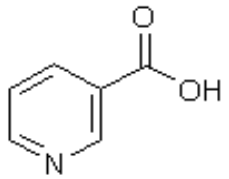
Tocotrienol



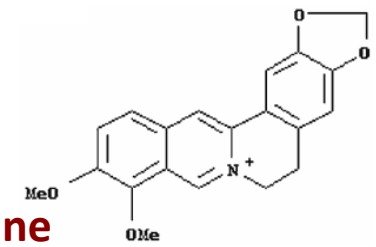
EPA

DHA

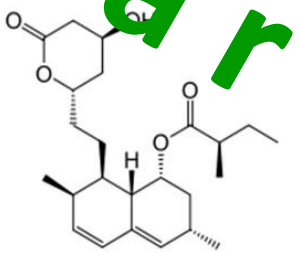
Niacin



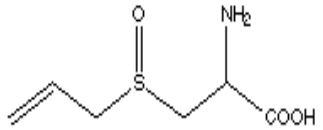
Berberine



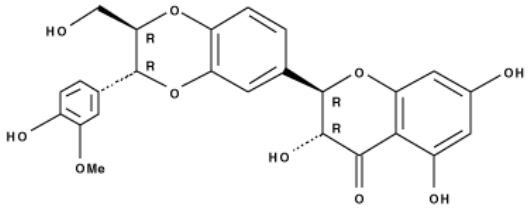
Monacolin K



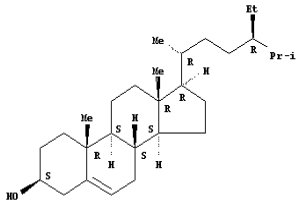
Alliin



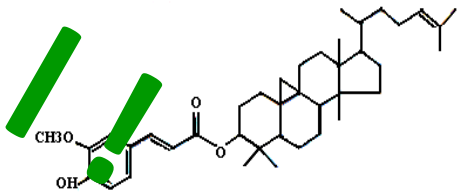
Silymarin



Phytosterols



γ-oryzanol



Nutrition, Metabolism & Cardiovascular Diseases (2023) **33**, 245–257

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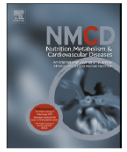
Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd



POSITION STATEMENT

LDL-cholesterol control in the primary prevention of cardiovascular diseases: An expert opinion for clinicians and health professionals

Andrea Poli [a,*], Alberico L. Catapano [b,c], Alberto Corsini [b], Enzo Manzato [d,e], José Pablo Werba [f], Gabriele Catena [g], Irene Cetin [h,i], Arrigo F.G. Cicero [j,k], Andrea Cignarella [d,l], Furio Colivicchi [m,n], Agostino Consoli [o,p], Francesco Landi [q,r], Maurizio Lucarelli [s], Dario Manfellotto [t,u], Walter Marrocco [v], Damiano Parretti [w], Pasquale Perrone Filardi [x,y], Angela Pirillo [c,z], Giorgio Sesti [aa,ab], Massimo Volpe [ac,ad], Franca Marangoni [a]

Table 1 Expected LDL-C reductions with the most commonly used cholesterol-lowering nutraceuticals and functional foods.

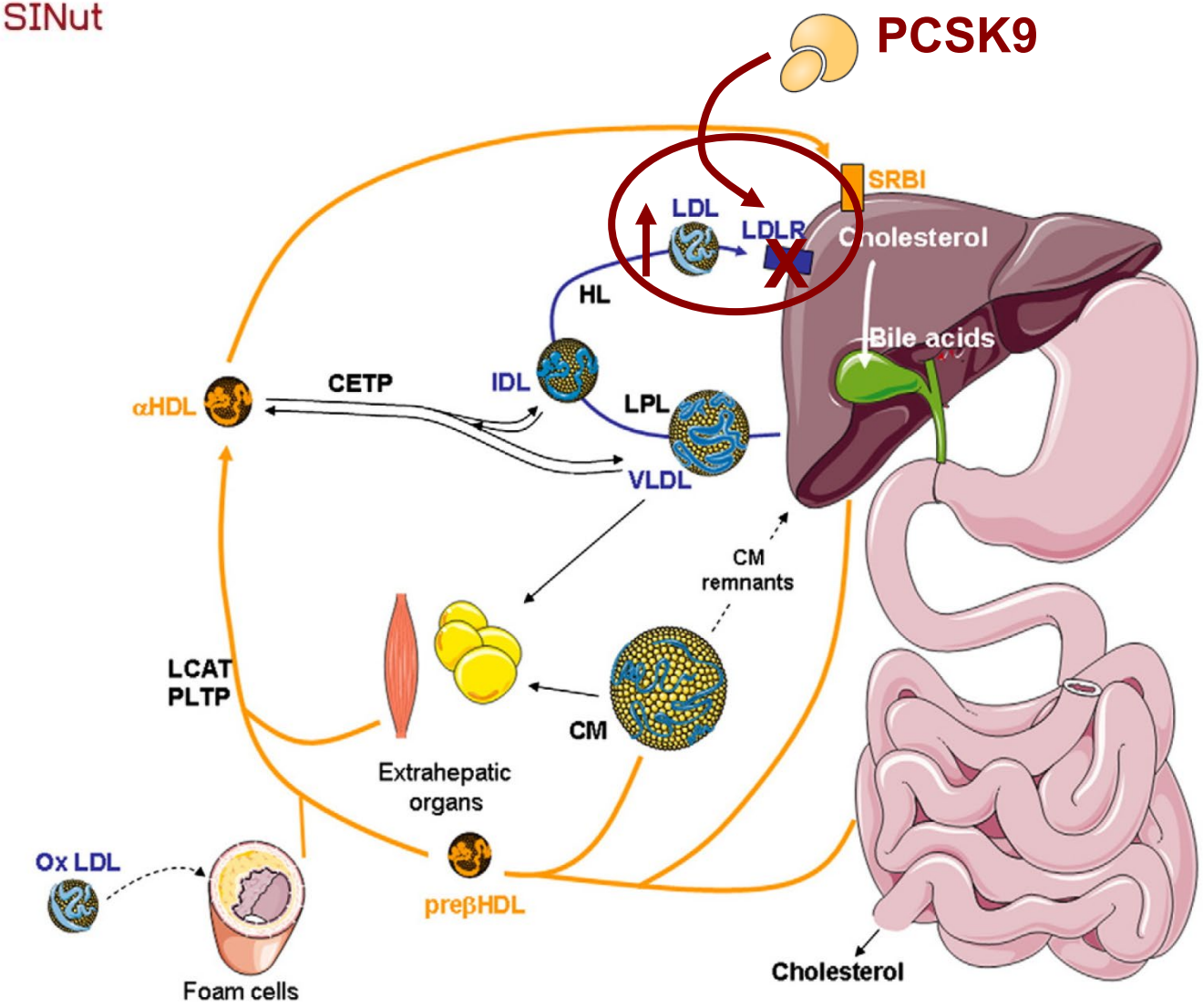
	Expected LDL-C reduction
Red yeast rice, titrated <3 mg in monacolin K/Ka	10–20%
Phytosterols/phytostanols	8–12%
Oat fibre	8–12%
Lactobacillus *spp.*	5–8%
Berberine	10–15%
Polyphenolic fraction of bergamot	10–12%
Artichoke standardized extract	10–12%

Modified from Cicero AFG et al., 2017 [101].

Poli A, et al. NMCD (2023) 33, 245e257

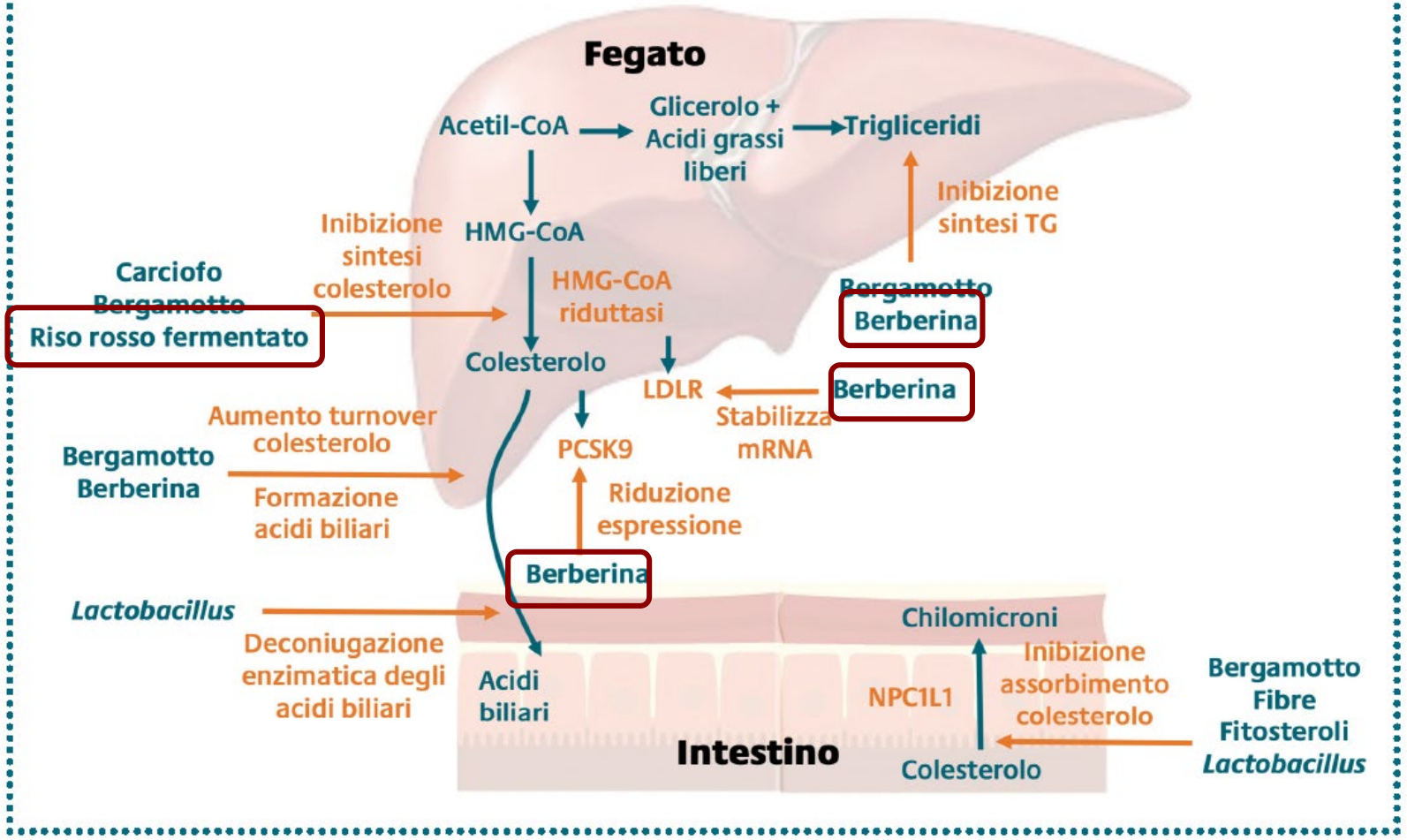
Main targets

- LDL receptor
- PCSK9



Costet P., *Pharmacology & Therapeutics* 126, 2010. 263–278
Lambert G. et *al*, *Atherosclerosis* 203, 2009 1–7

FIGURA 1 Meccanismi con cui i diversi nutraceutici esplicano l'azione ipolipemizzante



Ferri N et al, MEDICO e PAZIENTE | 6.2023

"*REGOLAMENTO (UE) 2024/2041 DELLA COMMISSIONE del 29 luglio 2024" che modifica il regolamento (UE) n. 432/2012 per quanto riguarda l'indicazione sulla salute riguardante la monacolina K da riso rosso fermentato"* in vigore dal 19 agosto 2024.

L'indicazione sulla salute "La monacolina K da riso rosso fermentato contribuisce al mantenimento di livelli normali di colesterolo nel sangue" non potrà pertanto essere più utilizzata.

In search of new hypocholesterolemic natural compounds

Bioactive alkaloids from Nepalese *Corydalis chaerophylla D.C.*

Kathmandu, Nepal

Phulchowki, Lalitpur, Nepal

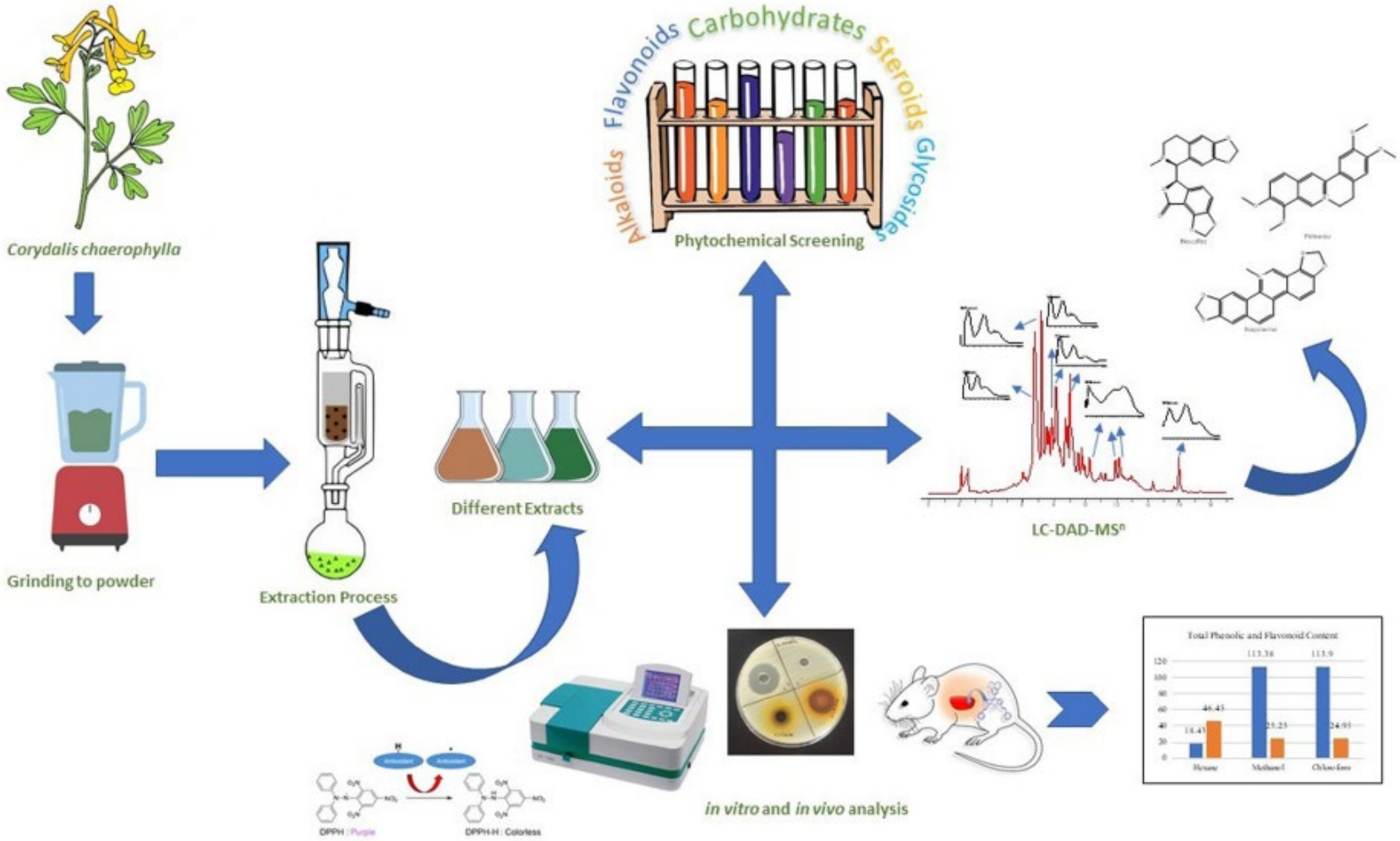
Corydalis chaerophylla D.C. is a glabrous herb found in high-altitude areas of Nepal, India, and Pakistan.

It survives in wet, shadowy conditions at elevations ranging from 2400 to 4800 a.l.s..

Corydalis chaerophylla was used as traditional medicine in Nepal for peptic ulcers

Corydalis chaerophylla D.C.

Chemical characterization of *Corydalis Chaerophylla* D.C. extracts



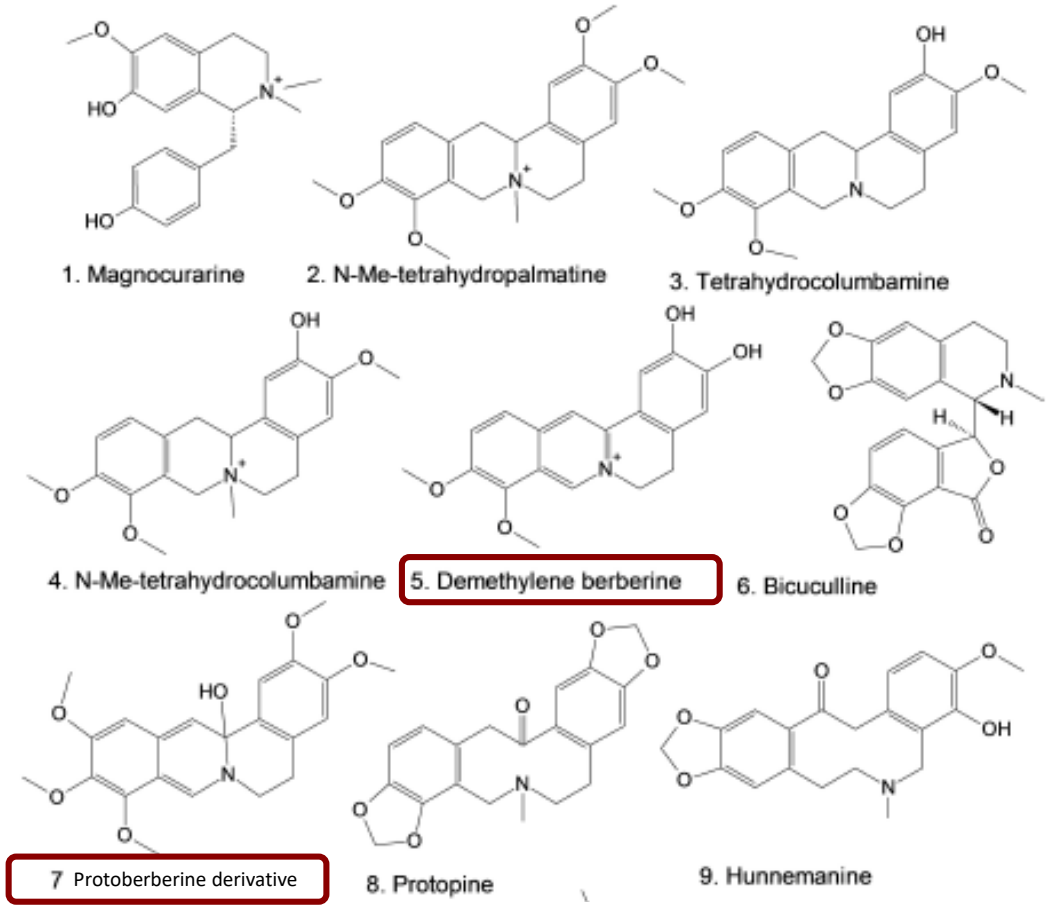
Chem. Biodiversity 2023, 20, e202301209

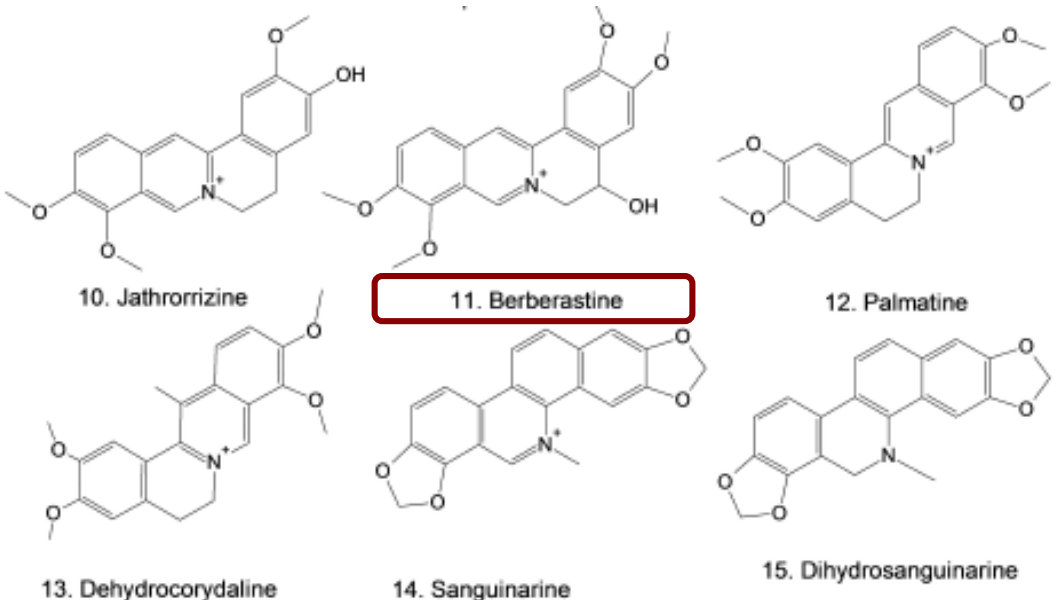
Table 2. Compounds observed in LC–DAD-MS of extracts of *C. chaerophylla*.

S.N.	Rt	m/z	Fragments	Compound	Extracts (mg/g)			Reference
					H	M	C	
1.	6.2	314	298.0, 269.0, 237.0, 175.0, 137.0, 107.0	Magnocurarine	–	0.12	0.08	[24]
2.	6.8	370	352.0, 334.0, 320.0, 290.0, 190.0, 175.0, 149.0, 131.0	N–Me-tetrahydropalmatine	0.77	23.31	218.01	
3.	8.53	340	178.0, 163.0	Tetrahydrocolumbamine	2.31	4.10	1.37	[25,26]
4.	8.58	356	192.0, 177.0, 148.0	N–Me-tetrahydrocolumb-amine	0.28	1.10	1.15	
5.	8.65	324	309	Demethylene berberine	4.26	12.48	45.38	
6.	8.84	368	307.0, 190.0	Bicuculline*	17.94	93.24	115.30	
7.	9.04	400	382.0, 355.0, 337.0, 319.0, 279.0	Protoberberine derivative	0.05	4.14	8.28	
8.	9.31	354	338.0, 190.0, 188.0, 149.0, 130	Protopine*	5.08	58.69	99.04	[24,27]
9.	9.34	356	338.0, 190.0	Hunnemanine	0.58	64.29	64.49	
10.	9.4	338	323.0, 294.0, 307.0, 279.0	Jatrorrhizine*	22.04	116.04	63.16	[24,25]
11.	9.5	368	338.0, 353.0, 321.0, 320.0, 307.0, 278.0	Berberastine	3.22	6.38	2.16	[24]
12.	9.76	352	336.0, 321.0, 308.0, 292.0, 278.0, 292.0, 275.0	Palmatine	3.30	8.30	2.09	[25,26]
13.	11.5	366	348.0, 323.0, 307.0, 190.0	Dehydrocorydaline	0.22	0.21	–	[25]
14.	15.8	332	317.0, 304.0, 274.0, 246.0	Sanguinarine*	1.88	2.52	0.36	[24,27]
15.	16.3	334	319.0, 304.0, 275.0, 246.0, 261.0	Dihydrosanguinarine	54.32	1.19	2.06	[24]

H: hexane, M: methanol, C: chloroform; compounds indicated with "*" were also confirmed by standard injection.

Structures of the identified alkaloids





Chem. Biodiversity 2023, 20, e202301209

Extraction and isolation of new alkaloids

1. Air dried powdered whole plant (10 kg) of *Corydalis chaerophylla* was cold percolated with hexane (20 L).

2. Plant residue was extracted with methanol (15 L) and concentrated up to 900 g of extract.

3. The methanol extract extracted with chloroform (120 g) and subjected to column chromatography by using:

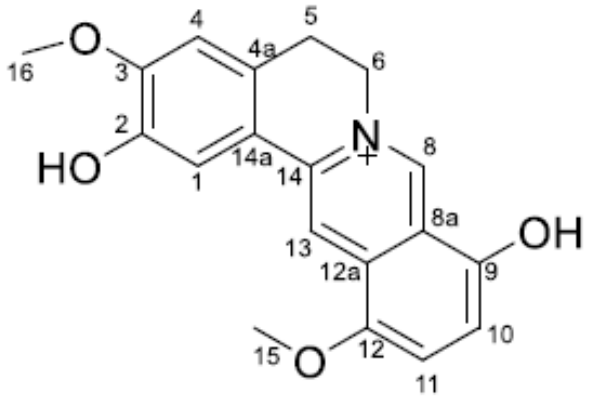
   3a. Ethyl acetate/hexane (0.5/95.5 - fraction A); ethyl acetate/hexane (5/95 - fraction B); ethyl acetate/hexane (10/90 - fraction C); chloroform/methanol (90/10 – fractions D and E).

   3b. Fraction E was subjected to silica gel column chromatography by using a dichloromethane (DCM)/methanol (95/5) solvent.

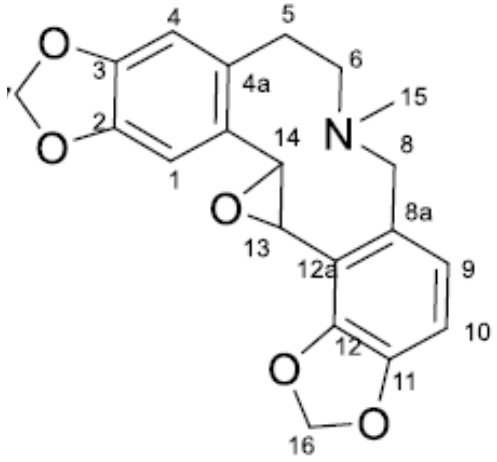
4. A total of 11 sets of fractions (E1-E11) were collected, which yielded four new compounds.

Chem. Biodiversity 2024, e202401388

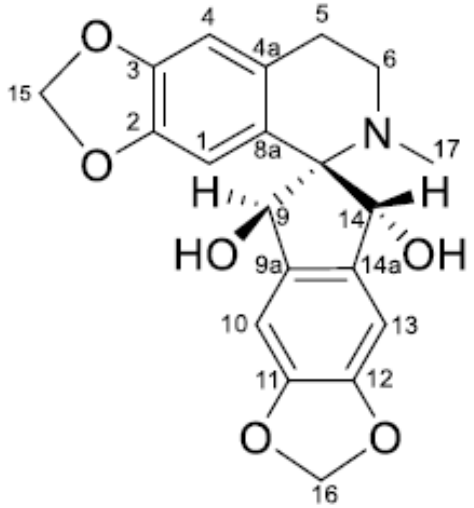
Chemical structures of four new alkaloids from *Corydalis Chaerophylla* D.C.



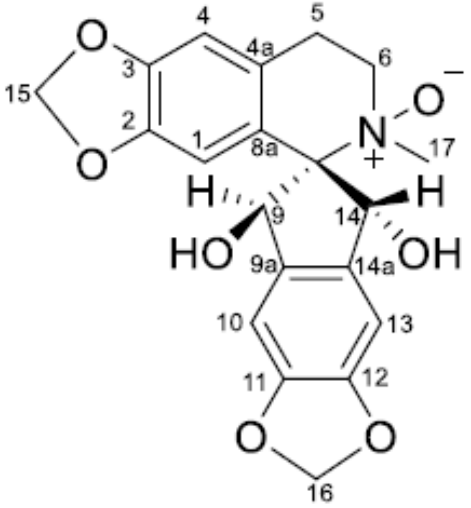
Chaeronepaline-A (**1**)



Chaeronepaline-B (**2**)



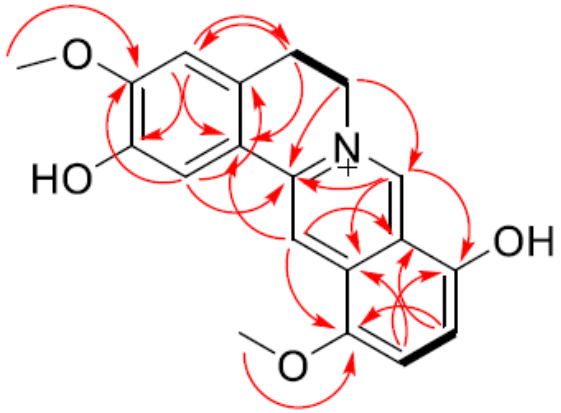
Chaeronepaline-C (**3**)



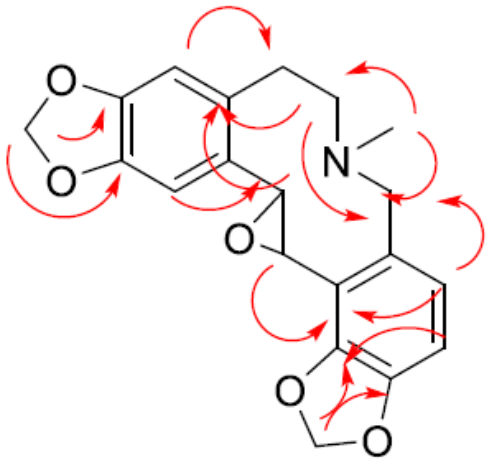
Chaeronepaline-D (**4**)

Chem. Biodiversity 2024, e202401388

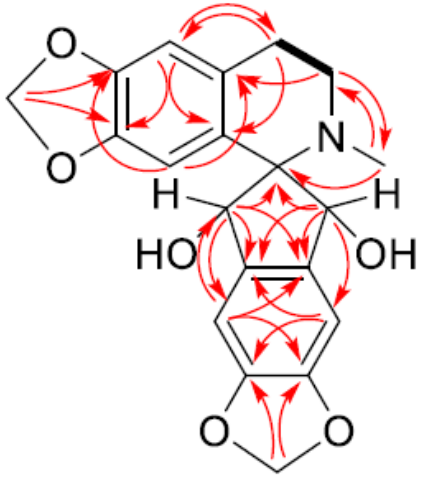
HMBC (red arrows), ^{1}H-^{1}H COSY (bold) correlation of compounds 1 - 4



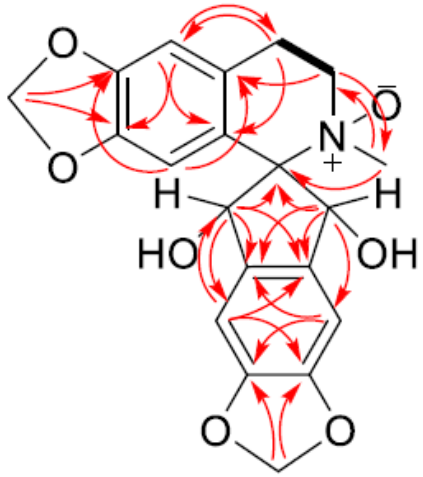
Chaeronepaline-A (**1**)



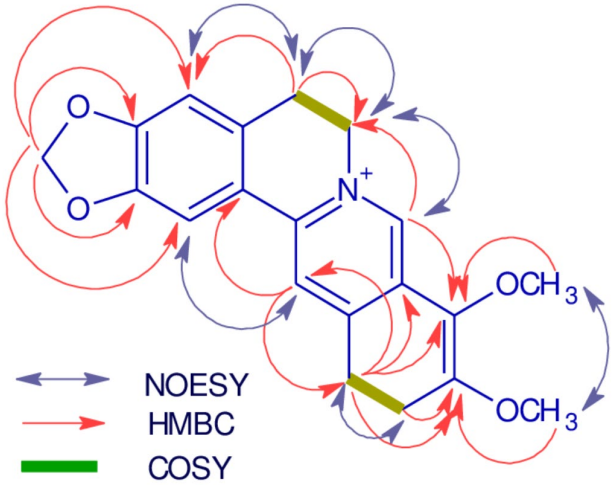
Chaeronepaline-B (**2**)



Chaeronepaline-C (**3**)



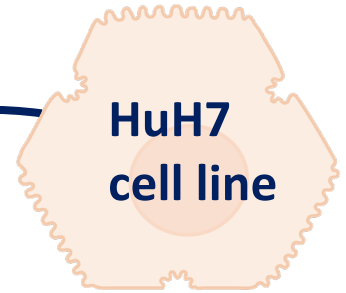
Chaeronepaline-D (**4**)



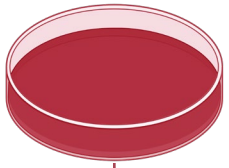
Berberine

Chem. Biodiversity 2024, e202401388

Methods

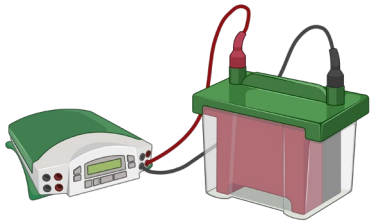


Day 0
Seeding

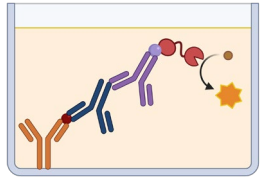


Day 1
Treatment

Day 3
Analysis

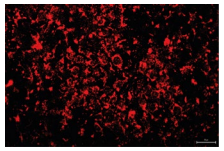


PCSK9 and LDL receptor expression



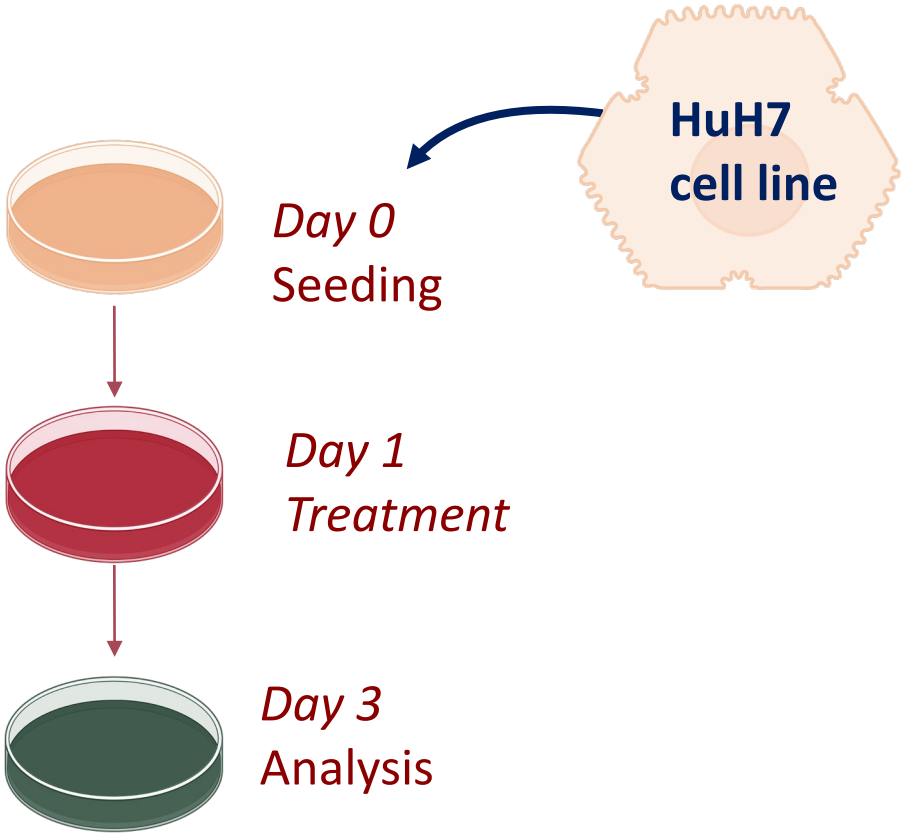
ELISA assay forPCSK9

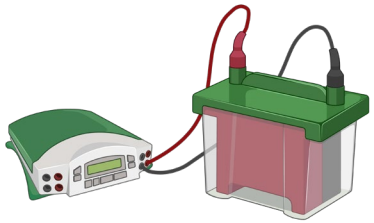
Cholesterol biosynthesis



Oil-RedO staining

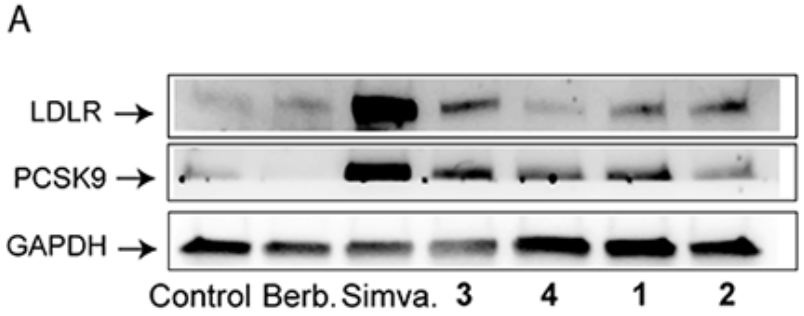
Methods

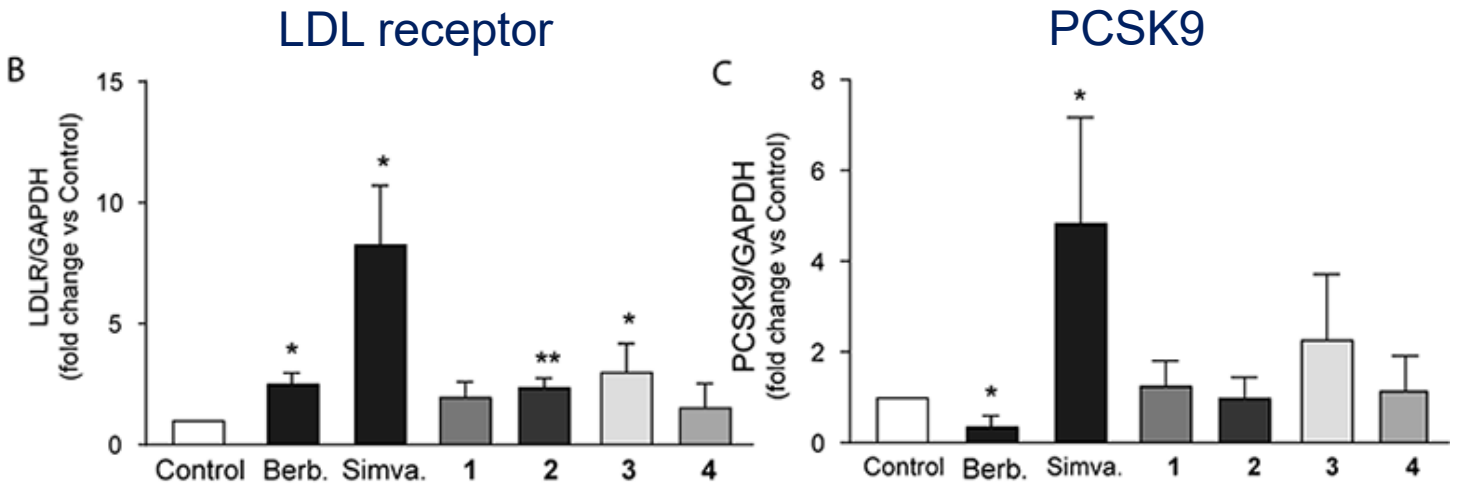




PCSK9 and LDL
receptor expression

Effect of alkaloids from Nepalese *Corydalis chaerophylla* D.C. on LDL receptor and PCSK9 expression in Huh7 cell line

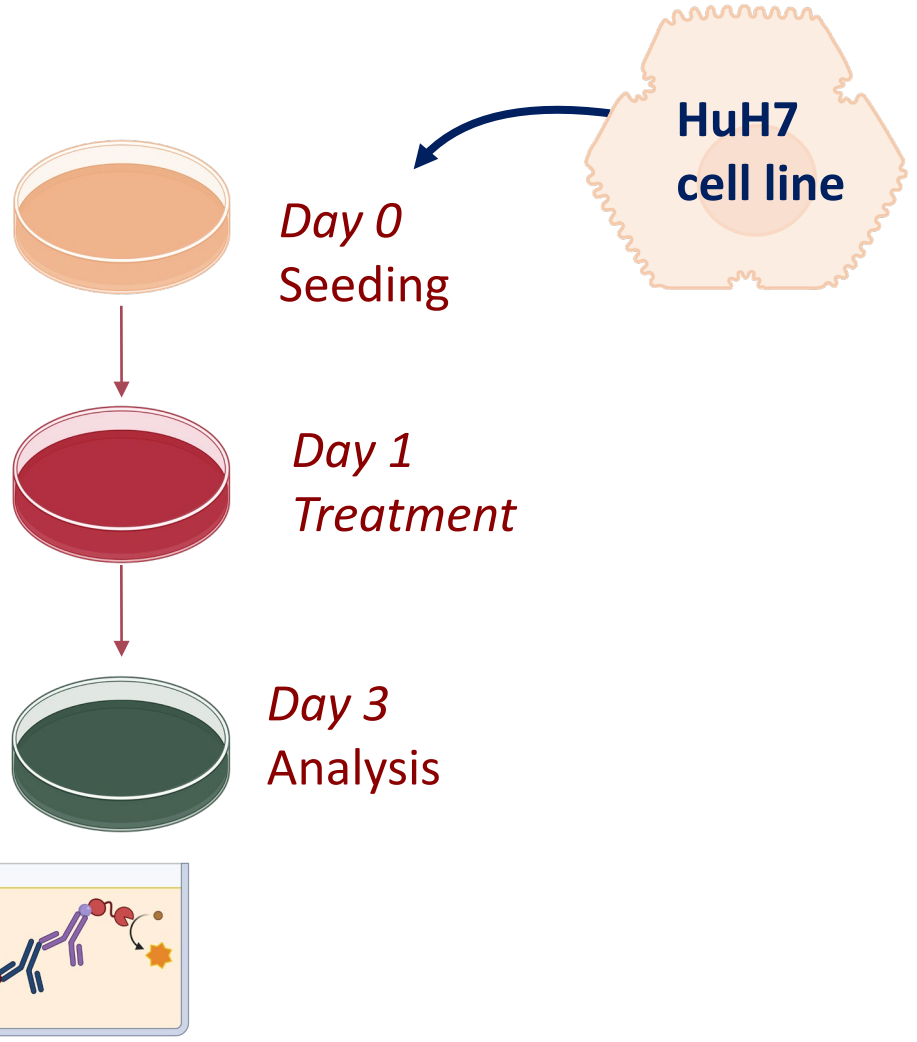




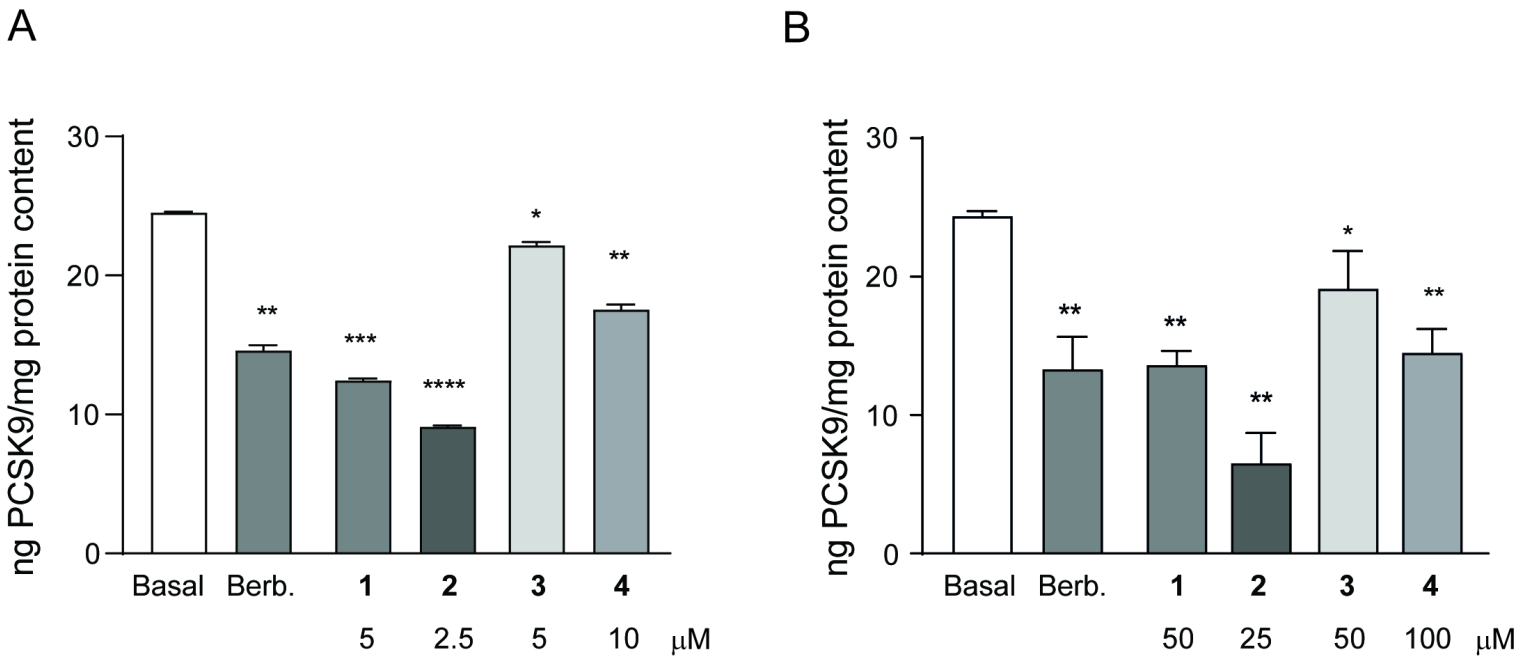
Chaeronepaline-A (**1**)
Chaeronepaline-B (2)
Chaeronepaline-C (3)
Chaeronepaline-D (**4**)

Chem. Biodiversity 2024, e202401388

Methods


HuH7
cell line
Day 0
Seeding
Day 1
Treatment
Day 3
Analysis
ELISA assay
forPCSK9

Effect of alkaloids from Nepalese *Corydalis chaerophylla* D.C. on PCSK9 secreted by Huh7 cell line

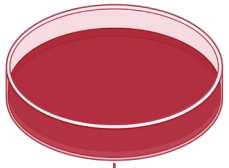


Chaeronepaline-A (**1**)
Chaeronepaline-B (2)
Chaeronepaline-C (**3**)
Chaeronepaline-D (**4**)

Chem. Biodiversity 2024, e202401388

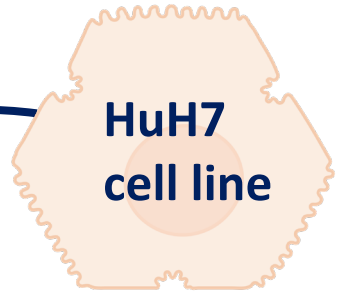
Methods

Day 0
Seeding



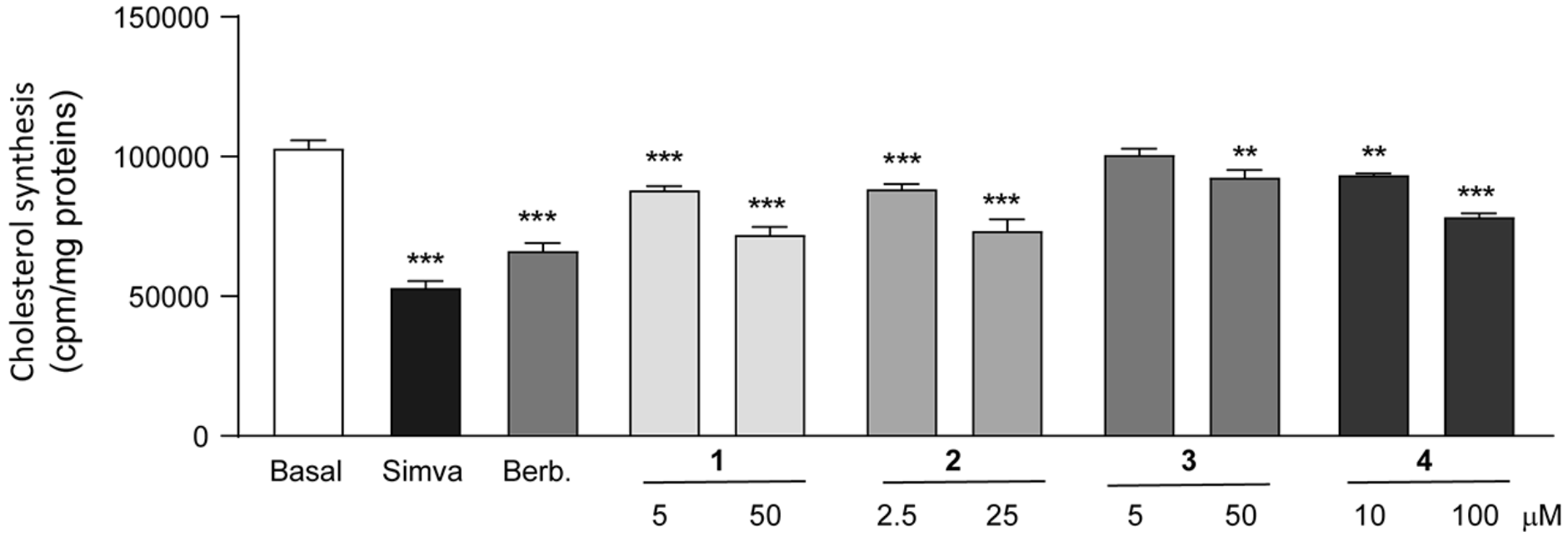
Day 1
Treatment

Day 3
Analysis



Cholesterol
biosynthesis

Effect of alkaloids from Nepalese *Corydalis chaerophylla* D.C. on cholesterol biosynthesis in Huh7 cell line

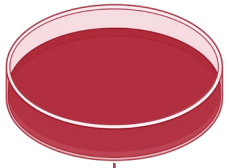


Chaeronepaline-A (1)
Chaeronepaline-B (2)
Chaeronepaline-C (**3**)
Chaeronepaline-D (**4**)

Chem. Biodiversity 2024, e202401388

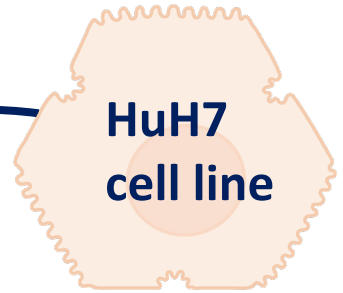
Methods

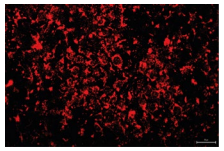
Day 0
Seeding



Day 1
Treatment

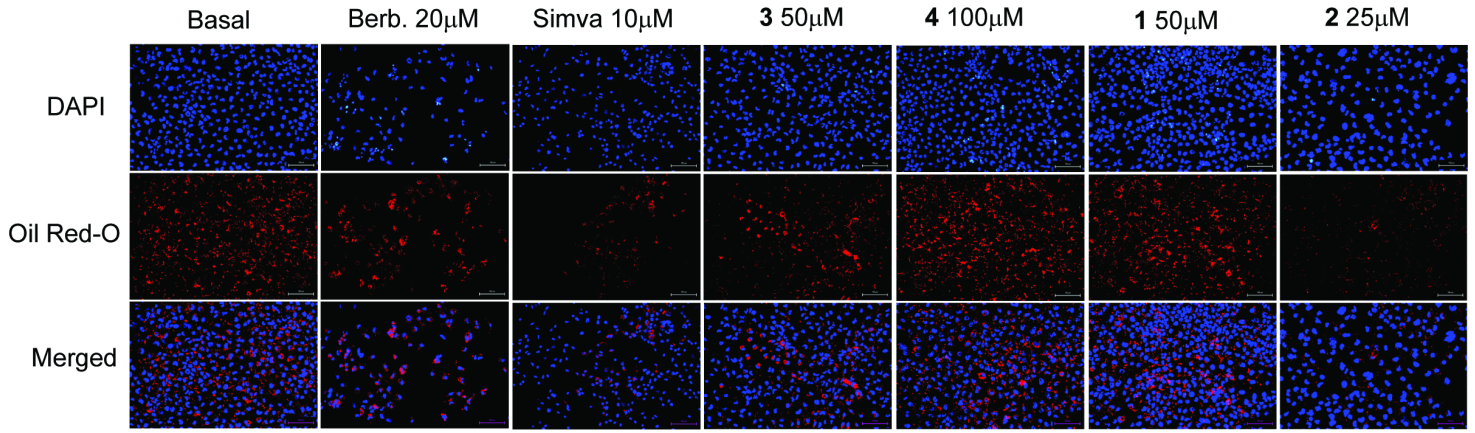
Day 3
Analysis

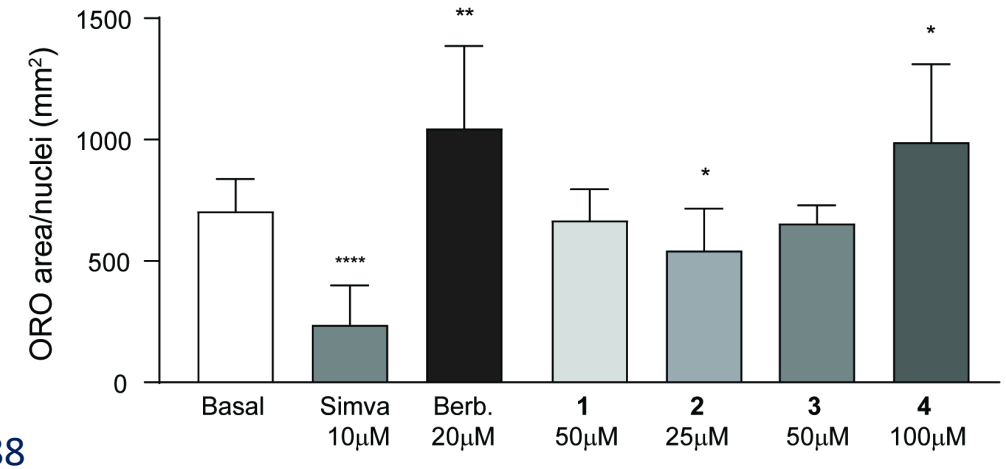




Oil-RedO
staining

Effect of alkaloids from Nepalese *Corydalis chaerophylla* D.C. on neutral lipid accumulation in Huh7 cell line





Chaeronepaline-A (**1**)
Chaeronepaline-B (2)
Chaeronepaline-C (**3**)
Chaeronepaline-D (**4**)

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Conclusions

The Nepalese *C. chaerophylla* D.C. was subjected to detailed phytochemical analysis.

Four new alkaloids were isolated, and their structures were established.

The new compounds were assayed on key proteins involved in cholesterol metabolism and Chaeronepaline-B (**2)** expressed the most promising activity by:

1) Inhibiting cholesterol biosynthesis
2) Reducing intracellular lipid accumulation
3) Decreasing PCSK9 secretion and secretion
4) Increasing LDL receptor levels of expression