14° CONGRESSO NAZIONALE SINut

SINut Società Italiana di Nutraceutica

12-14 settembre 2024

Bologna

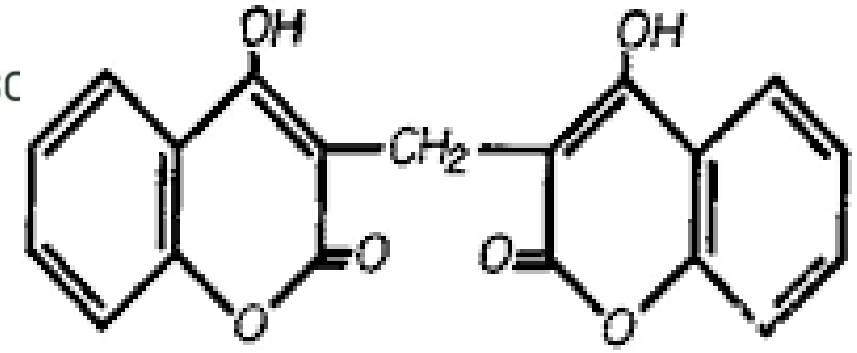
Identificazione degli attivi

Luigi Milella

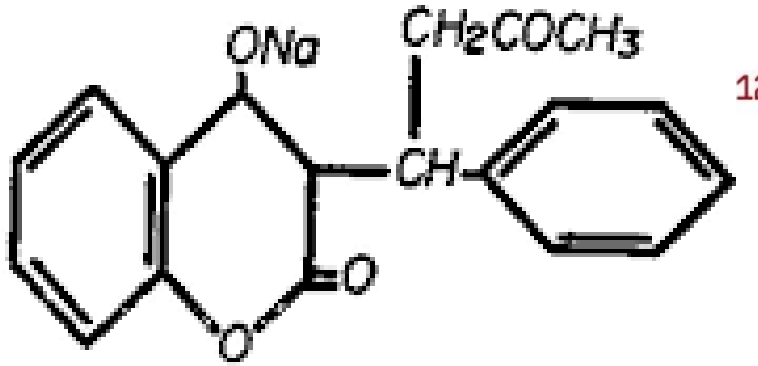
Università degli Studi della Basilicata

Approccio osservazionale…

Karl Paul Link ed un suo studente, Eugen Wilhelm Schoeffel



DICUMAROL



WARFARIN SODIUM

The NEW ENGLAND JOURNAL of MEDICINE

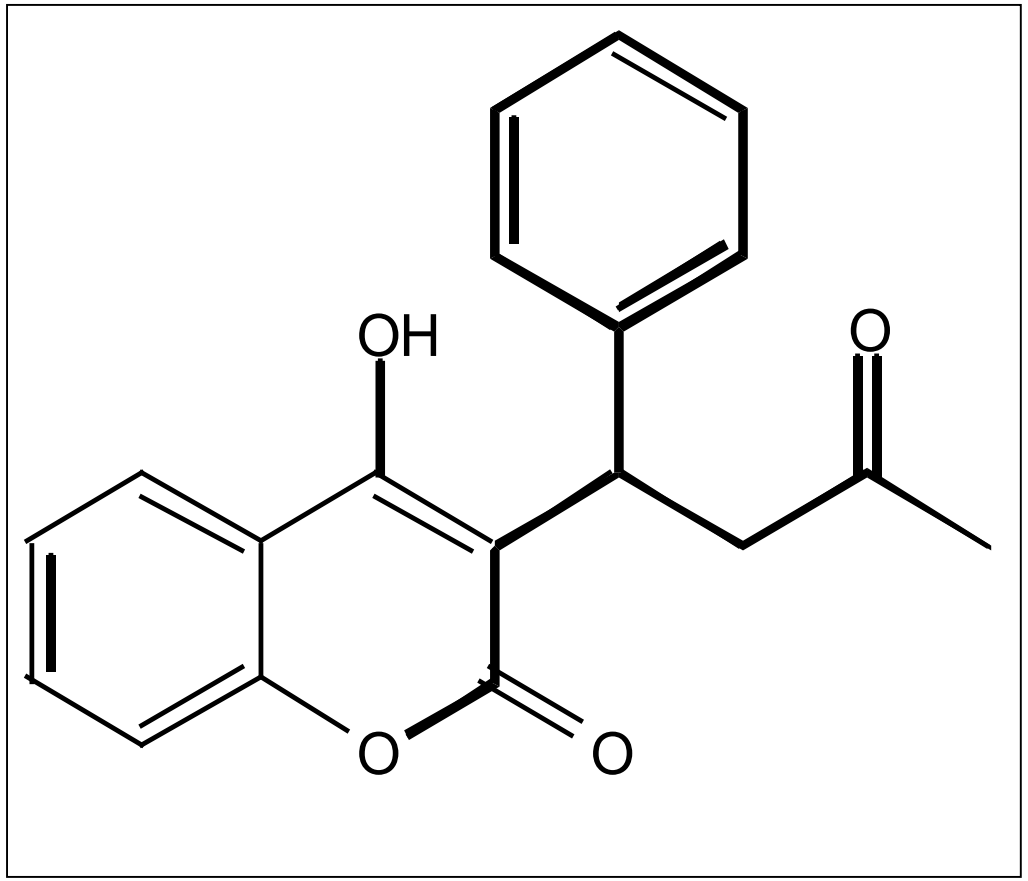
ORIGINAL ARTICLE | ARCHIVE

Coumadin (Warfarin) Sodium — A New Anticoagulant

Authors: Joseph H. Nicholson, M.D., and Thomas Leavitt, Jr., M.D. Author Info & Affiliations

Published September 13, 1956 | N Engl J Med 1956;255:491-501 | DOI: 10.1056/NEJM195609132551101
VOL. 255 NO. 11

Verso l'attività antigoagulante…



Wisconsin Alumni Research Foundation

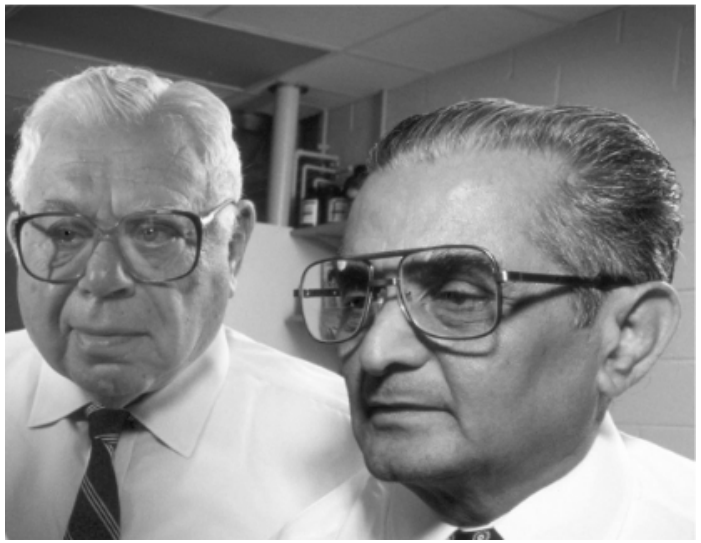
Eisenhower

Screening massale….

Il botanico Arthur Barclay con il cappello fotografa una collezione di piante sul campo, all'inizio degli anni '60.

Taxus brevifolia

Monroe Wall (sinistra)
Mansukh Wani (destra)



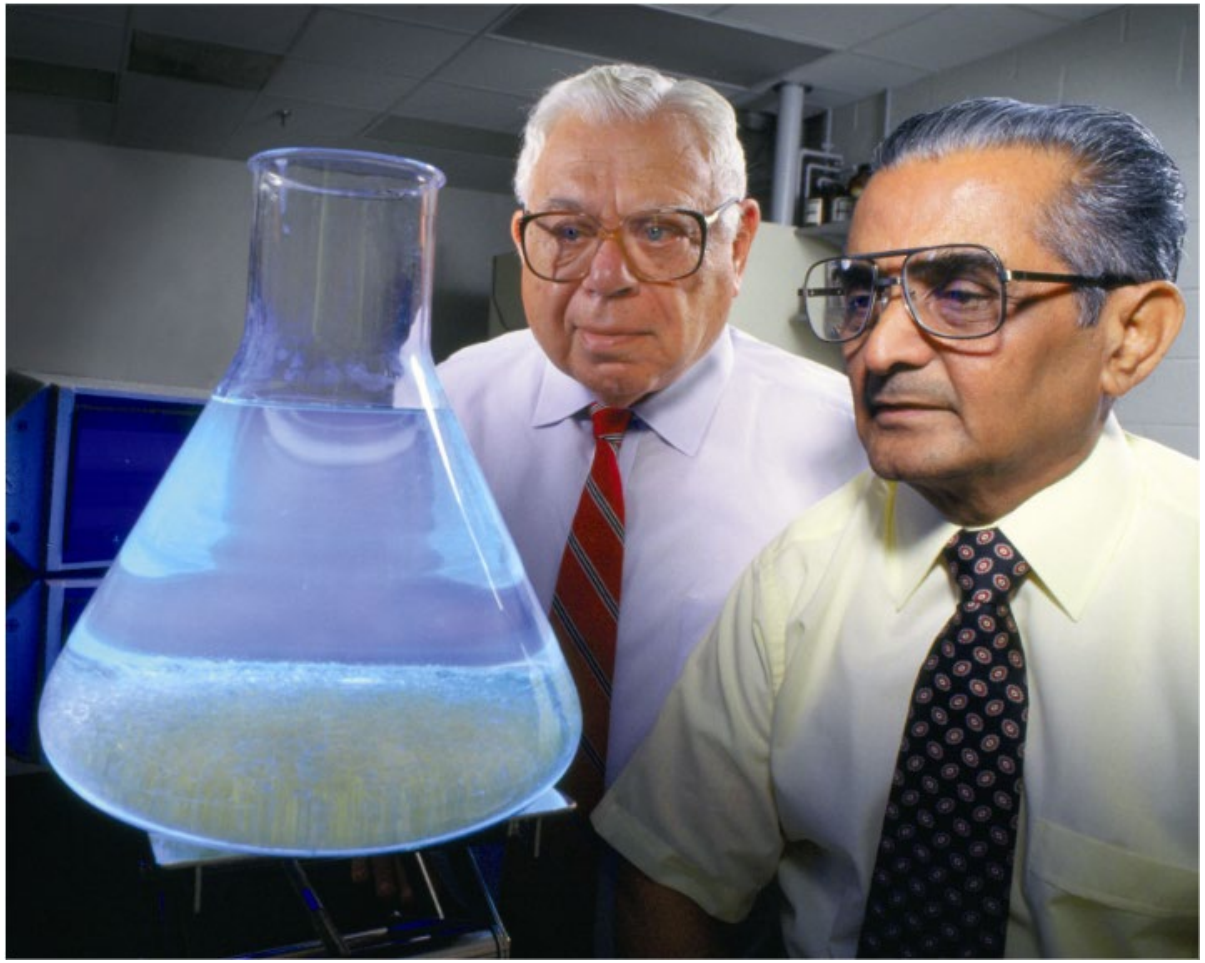
- Alla WARF Frazionamento degli estratti di *Taxus brevifolia* Nutt.

- La frazione «K172» mostrò attività contro la leucemia indotta nei topi.

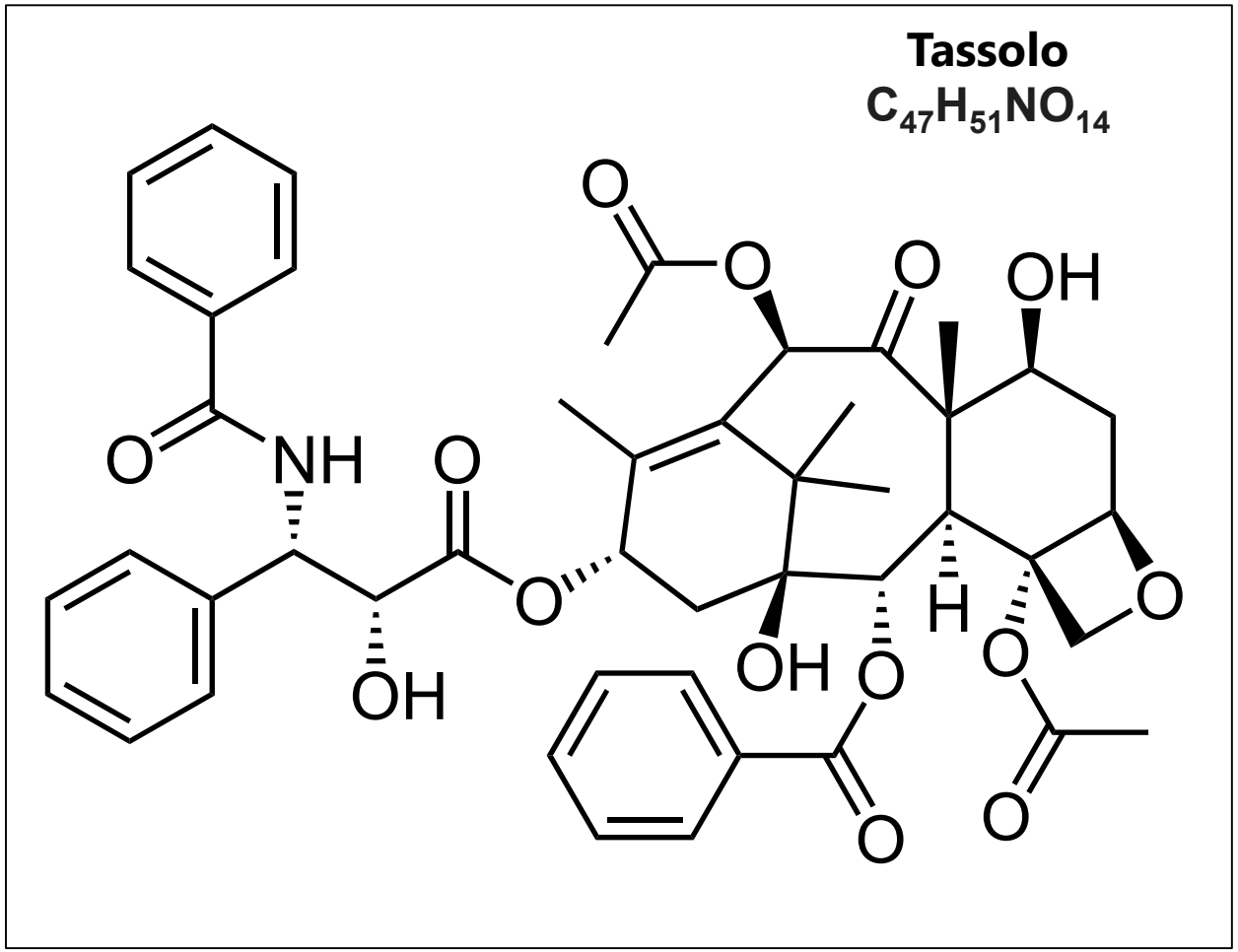
- Nel 1966, Wall chiedeva 170 kg di corteccia
- Da 12 kg di corteccia essiccata ricavava 0,5 grammi di «K172»

https://archive.ph/H0qQ

La scoperta del Tassolo nel 1967



Dr. **Monroe Wall** e Dr. **Mansukh Wani**



https://www.acs.org/education/whatischemistry/landmarks/camptothecintaxol.html

Verso l'attività antitumorale…

Susan B. Horwitz

Distinguished Professor at the Albert Einstein College of Medicine

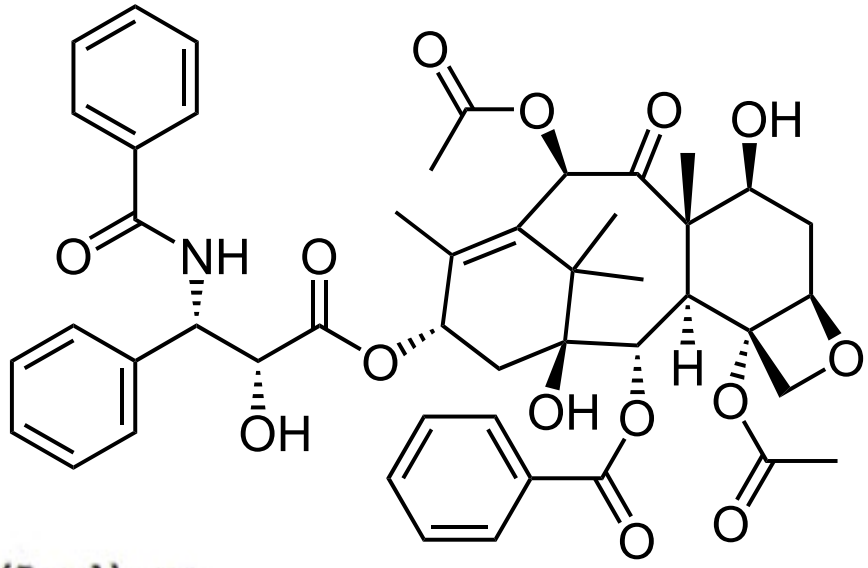
April 21, 1977

Dr. Susan Horwitz
Assistant Professor
Department of Pharmacology
Albert Einstein College of
Medicine of Yeshiva University
1300 Morris Park Avenue
Bronx, New York 10461

Dear Susan:

At a recent Decision Network meeting, NSC-125973 (Taxol) was approved for further study. We have some information about it (folder enclosed) and believe that it may be a protein synthesis inhibitor. Would you please study this compound in your systems.

The compound is quite insoluble in aqueous vehicle, but DMA and DMSO can be used effectively.



https://blogs.einsteinmed.edu/blog/2019/04/03/reflections-on-my-life-with-taxol/

1978, «Puoi aiutare questa povera ragazza?»

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY

1300 MORRIS PARK AVENUE. BRONX, N.Y. 10461. CABLE EINCOLLMED, N.Y.

DEPARTMENT OF MOLECULAR PHARMACOLOGY PHONE: (212) 430-2000

August 9, 1978

Dr. John Douros
Drug Development Branch
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

Dear John:

As I mentioned to you in Hawaii, my laboratory has become very interested in the mechanism of action of taxol. We have been working intensely with this drug during the past year and find that it is extremely cytotoxic to cells growing in culture. Although we have not completely defined its site of action, we know that it is quite different from any other drug that we have previously studied and we plan to pursue its activity. In order to do this, we need radio-actively labeled taxol. Monroe Wall and M.C. Wani isolated taxol and would certainly be the most knowledgeable concerning the preparation of labeled drug. I would, of course, include them in any publications that might develop from material they prepared. I would appreciate it if you could bring this problem to their attention. We would also like to test the two major products isolated from taxol after mild base-catalyzed methanolysis, $C_{17}H_{17}NO_4$ and $C_{29}H_{36}O_{10}$, as described in JACS 93:9, 1971.

I enjoyed talking with you in Hawaii. Thank you very much for your help.

Sincerely,

Susan

Susan B. Horwitz, Ph.D.
Associate Professor

SBH:mr

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL CANCER INSTITUTE

78

August 22, 1978

Dr. Monroe E. Wall
Research Triangle Institute
P. O. Box 12194
Research Triangle Park, NC 27709

Dear Monroe:

Can you help this poor girl (enclosed letter). Please send me a quote on these radiolabeled materials and I will buy them from you.

Sincerely,

John

John D. Douros, Ph.D.
Chief, Natural Products Branch
Developmental Therapeutics Program
Division of Cancer Treatment, NCI

enclosure

Dr Wani
Dr Kepler Roy Kelley

Meccanismo d'azione

Nature Vol. 277 22 February 1979

Promotion of microtubule assembly *in vitro* by taxol

TAXOL (Fig. 1) was isolated from the plant *Taxus brevifolia* (western yew) by Wani *et al.*, who reported that the molecule has antitumour activity in several experimental systems[1]. In our laboratory we have found that taxol, a low molecular weight neutral compound, completely inhibits division of exponentially growing HeLa cells at low concentrations of drug (0.25 μM) that have no significant effects on DNA, RNA or protein synthesis during a 4-h incubation with the cells. HeLa cells incubated with taxol for 20 h are blocked in late G_2 and/or M (ref. 2). We report here that taxol acts as a promoter of calf brain microtubule assembly *in vitro*, in contrast to plant products such as colchicine and podophyllotoxin, which inhibit assembly. Taxol decreases the lag time for microtubule assembly and shifts the equilibrium for assembly in favour of the microtubule, thereby decreasing the critical concentration of tubulin required for assembly. Microtubules polymerised in the presence of taxol are resistant to depolymerisation by cold (4 °C) and $CaCl_2$ (4 mM).

Many models have been proposed for the microtubule assembly system used in these experiments[3], but the exact mechanism for microtubule assembly *in vitro* is not known; the conditions required have been described elsewhere[4]. A dynamic equilibrium of microtubules with tubulin dimers has been demonstrated *in vitro*[5–7]. Our standard conditions for assembly in a final volume of 1.0 ml at 37 °C are: 1 mM EGTA, 0.5 mM $MgCl_2$, 1 mM GTP, 0.1 M 2-[*N*-morpholino]ethane sulphonic acid (MES) at *p*H 6.6 and 1 mg ml^{-1} tubulin.

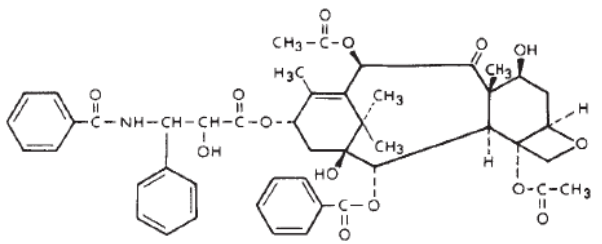
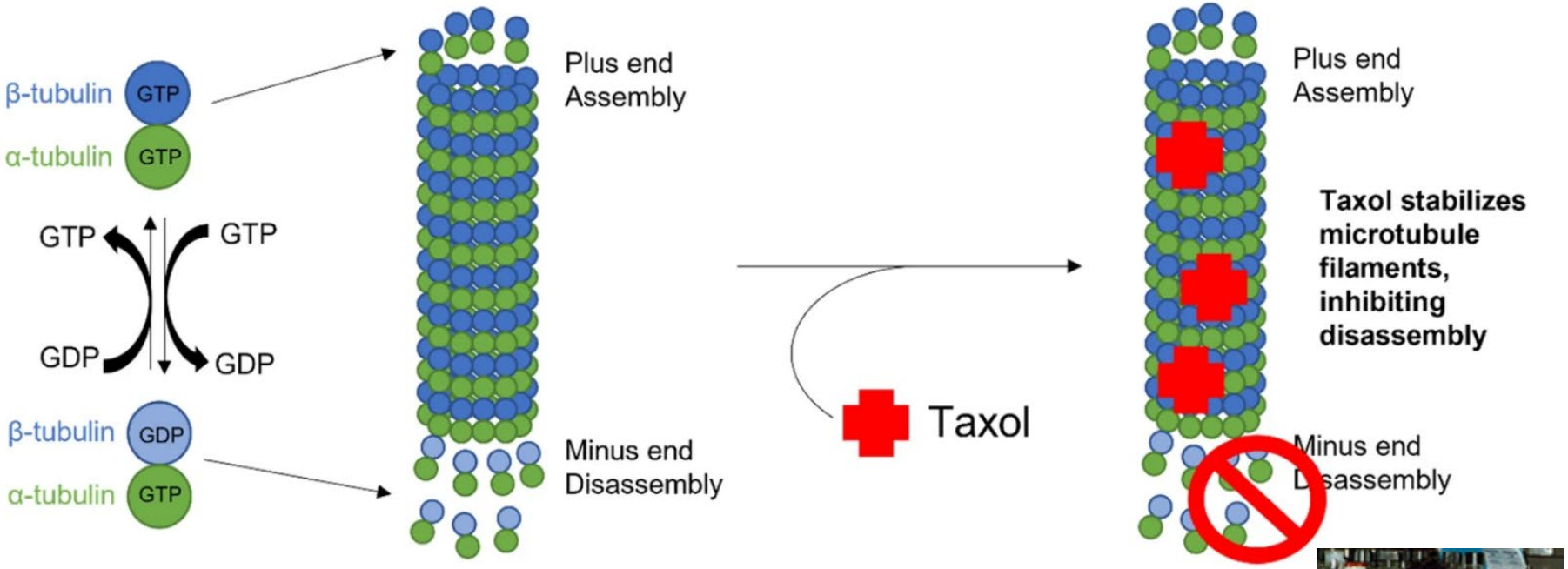


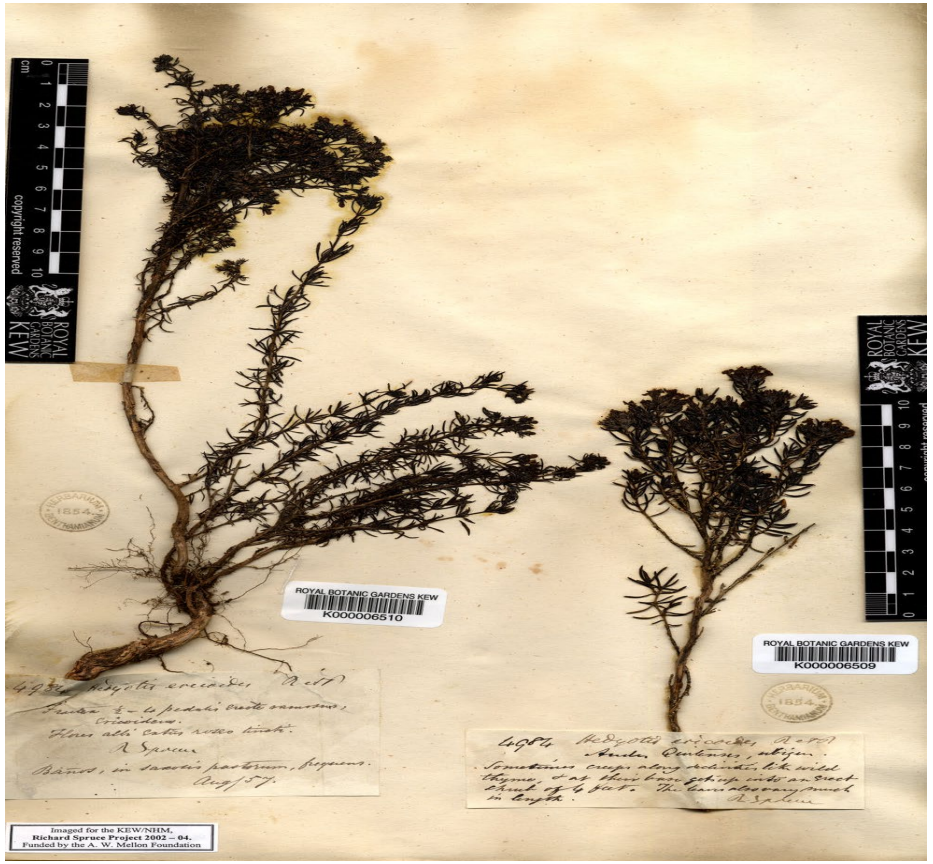
Fig. 1 Structural formula of taxol.

0028–0836/79/0277—0665$01.00



Susan B. Horwitz

Approccio Etnofarmacologico



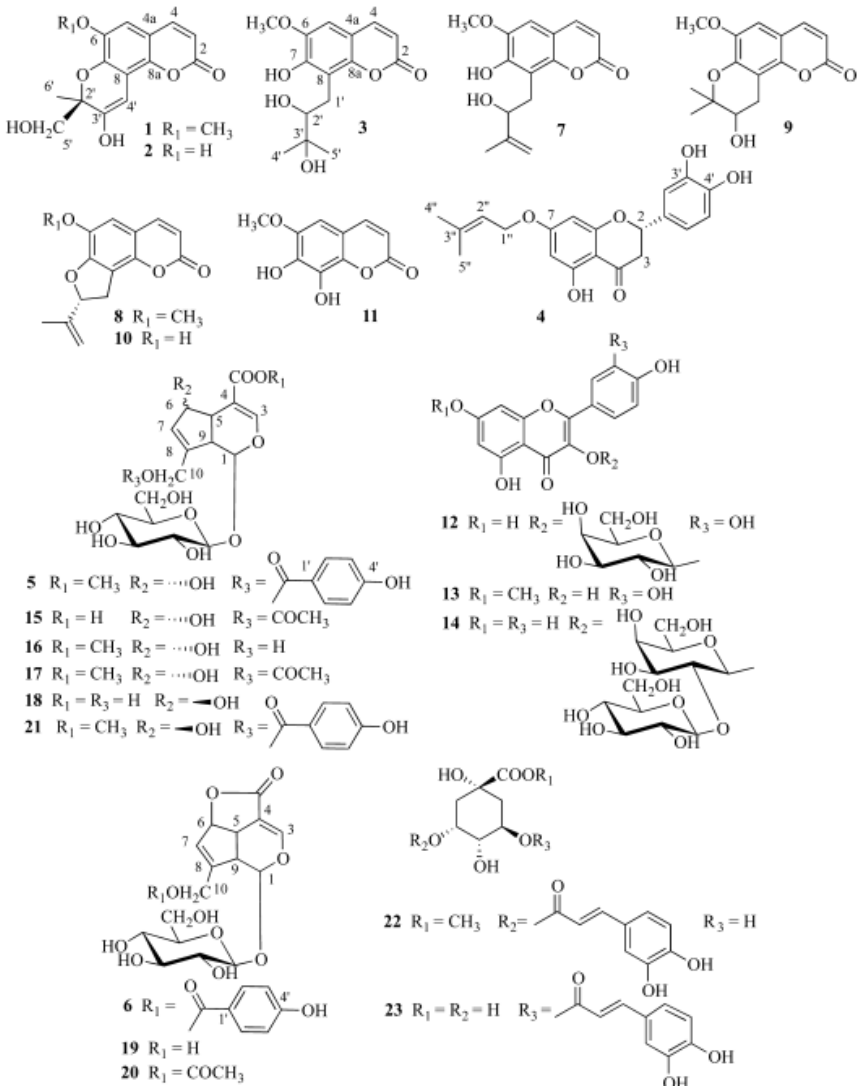
JOURNAL OF NATURAL PRODUCTS

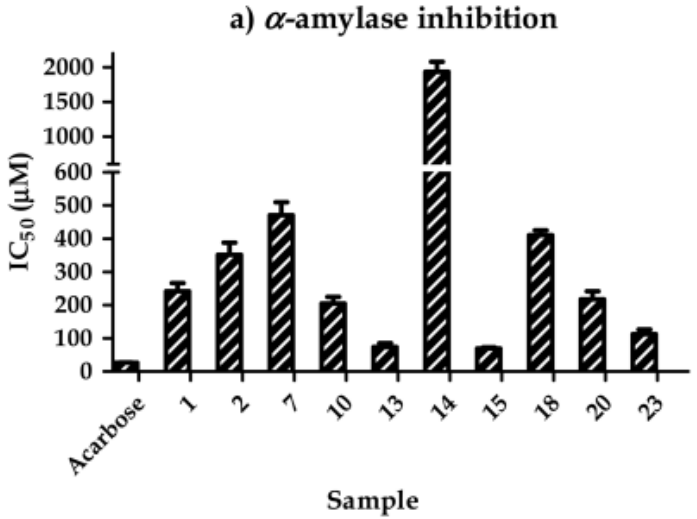
Article

pubs.acs.org/jnp

α-Glucosidase and α-Amylase Inhibitors from *Arcytophyllum thymifolium*

Luigi Milella,[†] Stella Milazzo,[‡] Marinella De Leo,[‡] Mariela Beatriz Vera Saltos,[⊥] Immacolata Faraone,[†] Tiziano Tuccinardi,[‡,§] Margherita Lapillo,[‡] Nunziatina De Tommasi,[*,∥] and Alessandra Braca[‡,§]





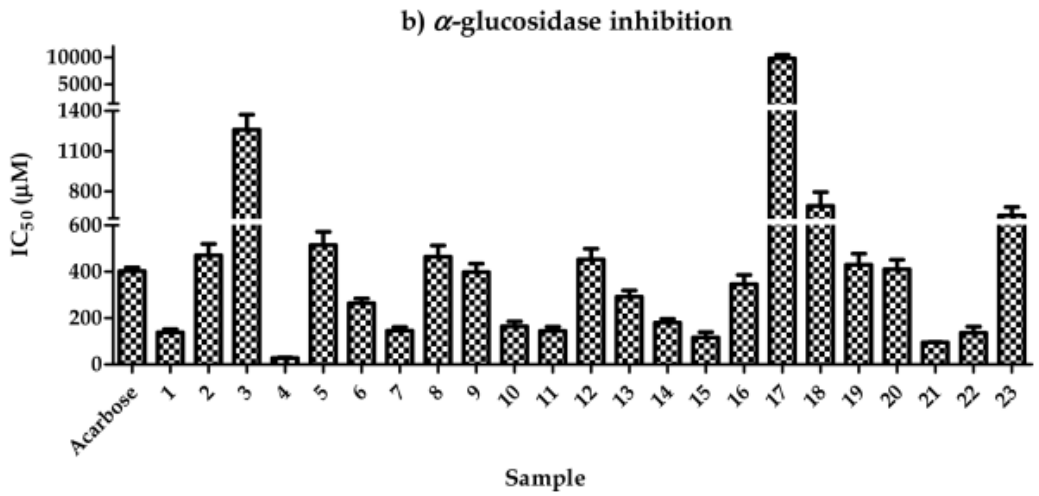
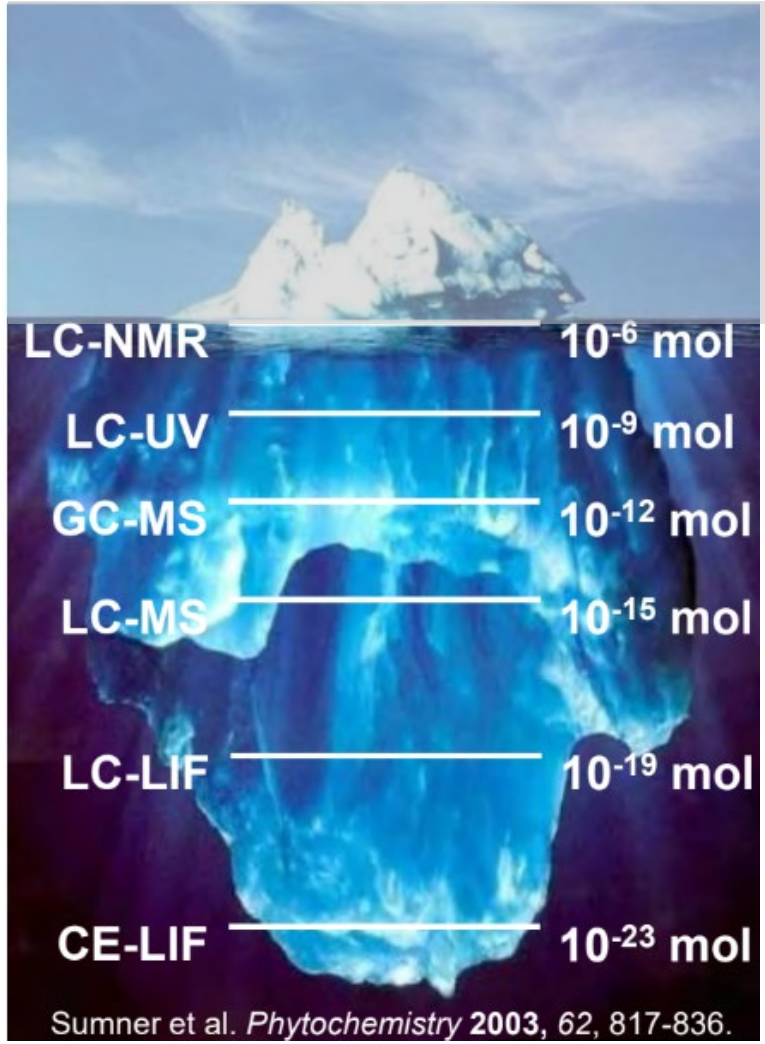


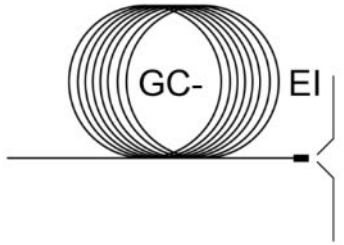
Figure 1. (a) α-amylase and (b) α-glucosidase inhibition (IC_{50} values in μM, data are means ± SD from three experiments) by acarbose and the isolated compounds (**1**–**23**).

Evoluzione delle macchine…

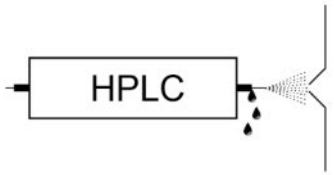


Estrazione → Frazioni attive → Puro

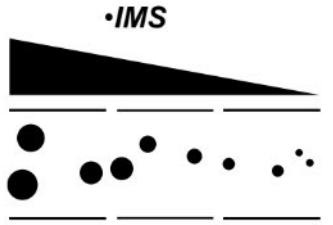
GC-EI-MS



LC-MS



IMS-MS

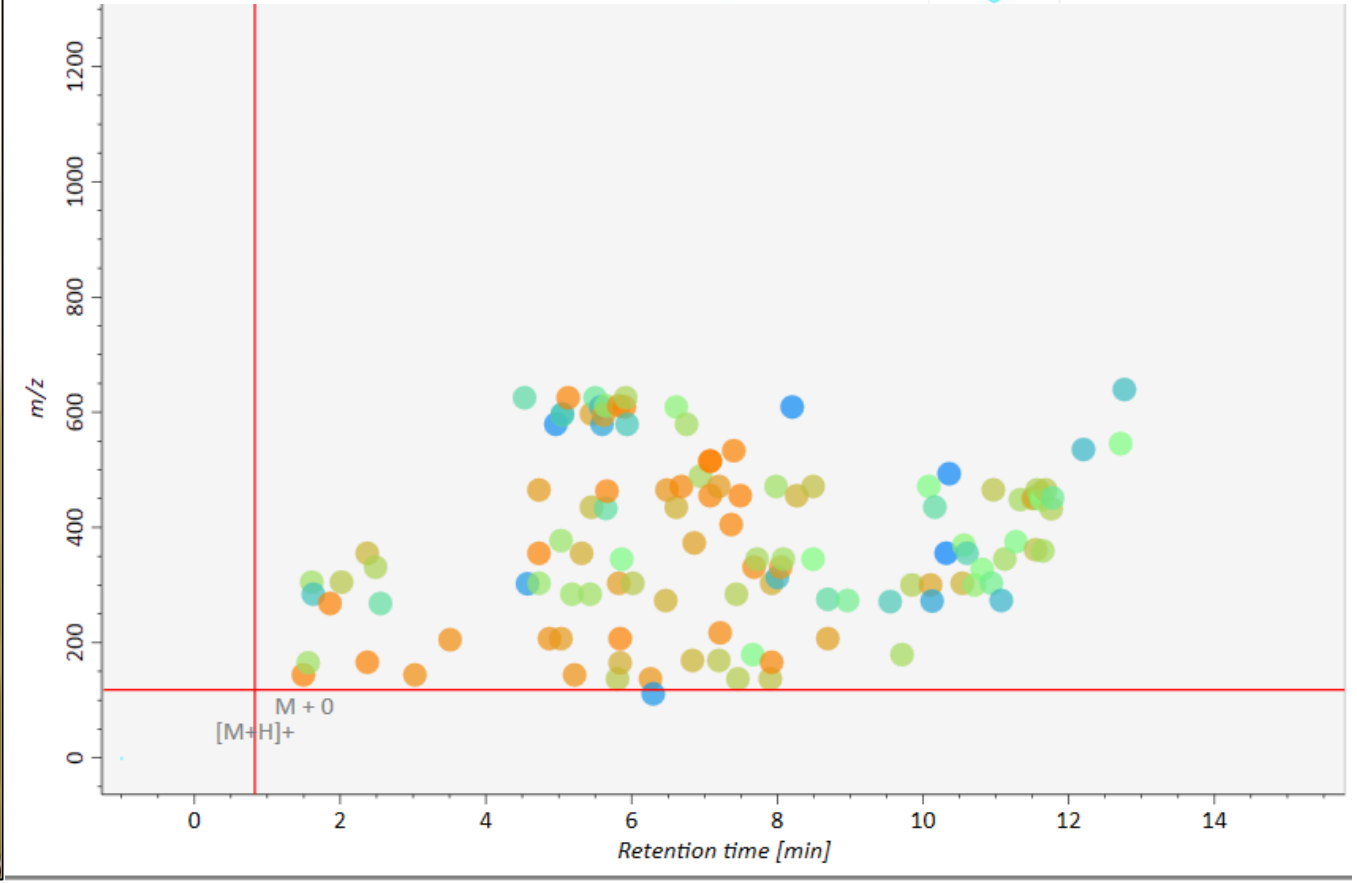


Target screening

LIMITI
- Librerie

VANTAGGI
- Quantificazione assoluta
- Profilo completo di metaboliti noti

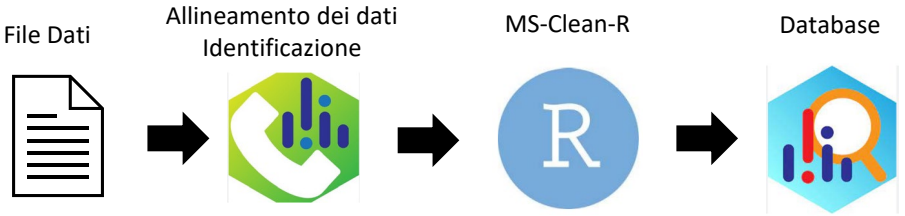
File Dati → Allineamento dei dati Identificazione → MS-Clean-R → Database

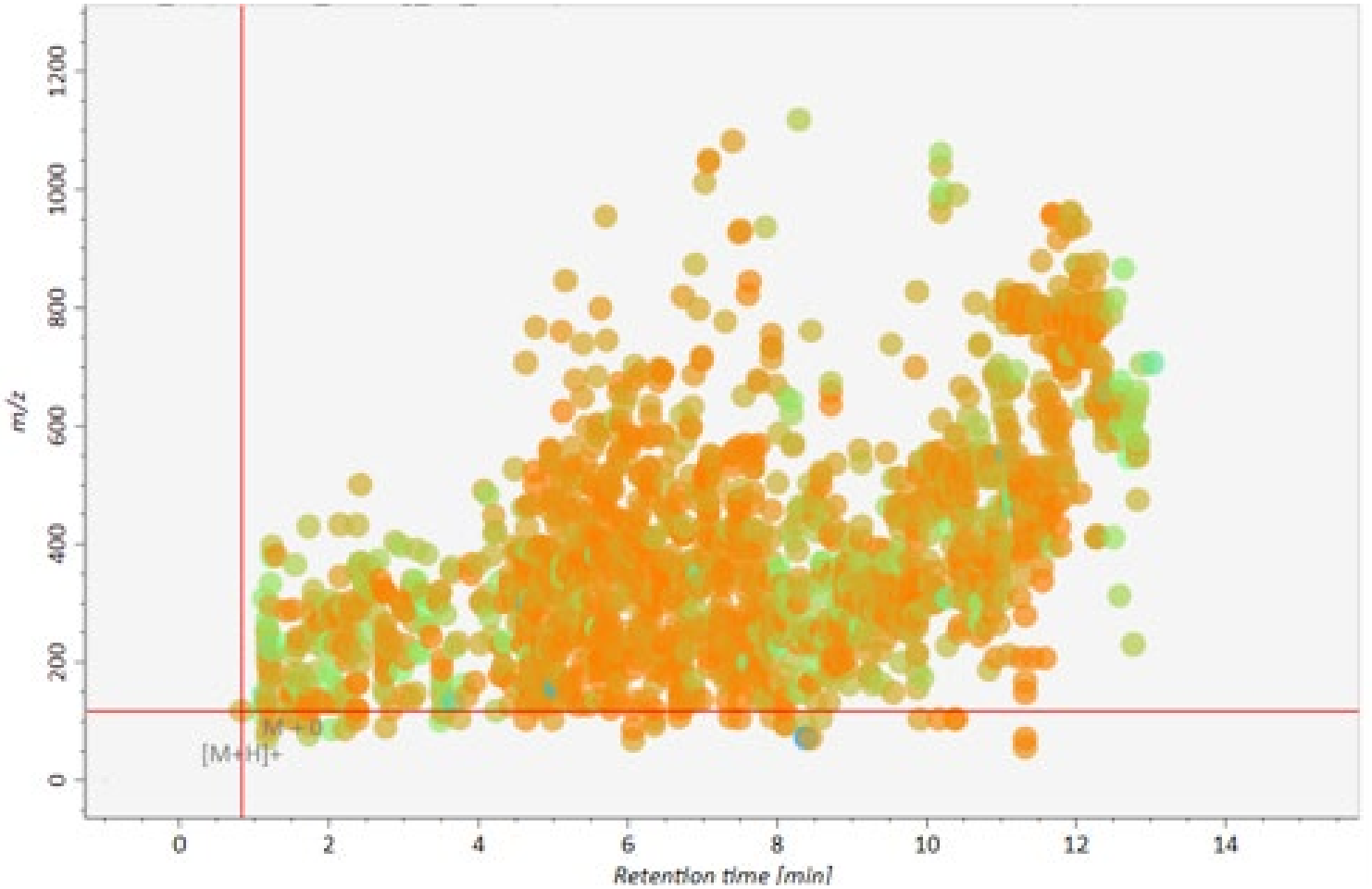


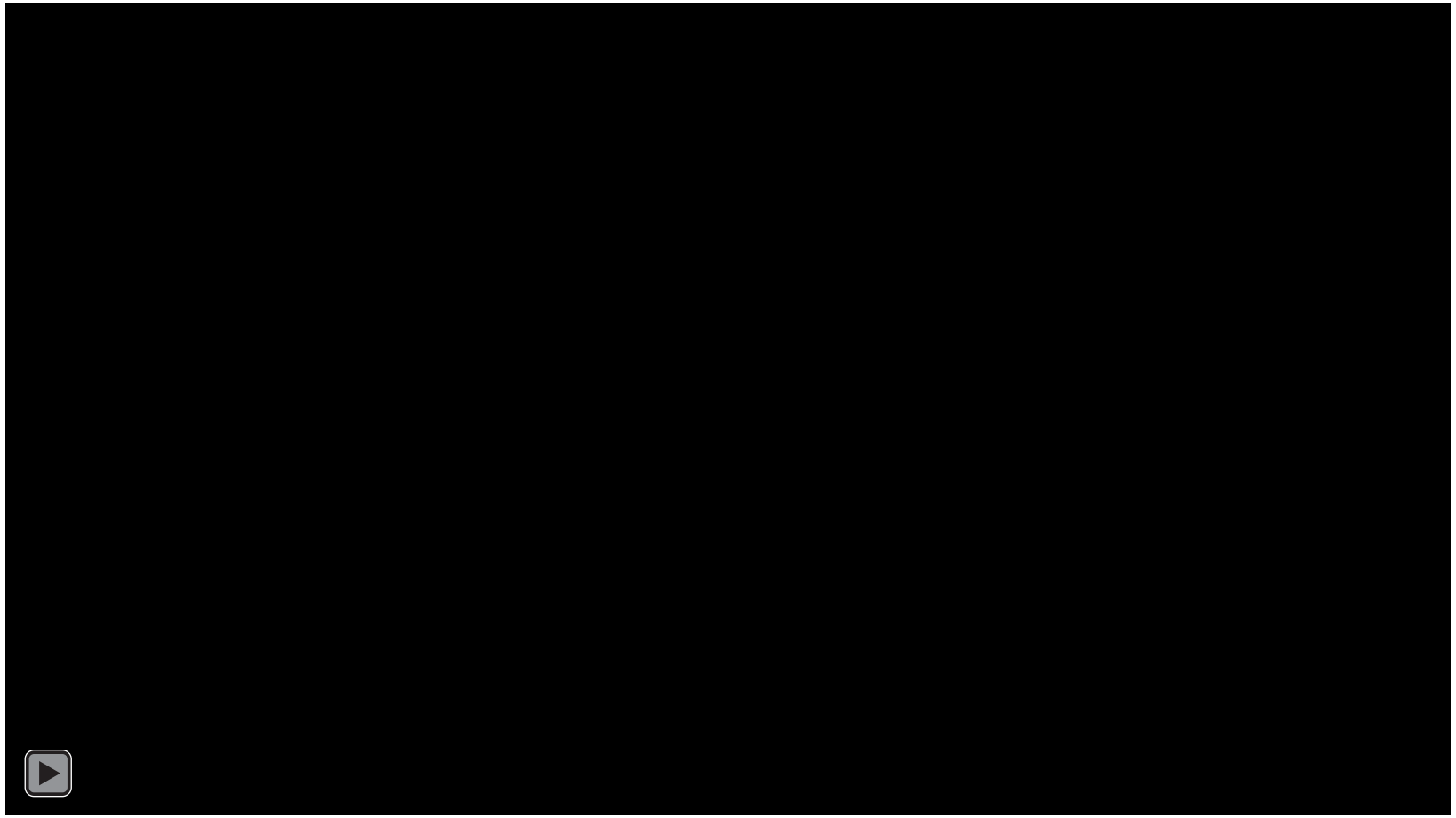
Non-target screening

LIMITI
- Quantificazione
- Identificazione

VANTAGGI
- Nuovi metaboliti







Gli strumenti parlano...DATI

antioxidants

MDPI

Academic Editor(s): Name

Received: 17 July 2024
Revised: 7 September 2024
Accepted: 9 September 2024
Published: date

Article

Extraction Optimization of *Quercus cerris* L. Wood Chips: A Comparative Study between Full Factorial Design (FFD) and Artificial Neural Network (ANN)

Maria Ponticelli [1,2], Vittorio Carlucci [1,*], Marisabel Mecca [3], Luigi Todaro [3], Luigi Milella [1,*] and Daniela Russo [1,*]

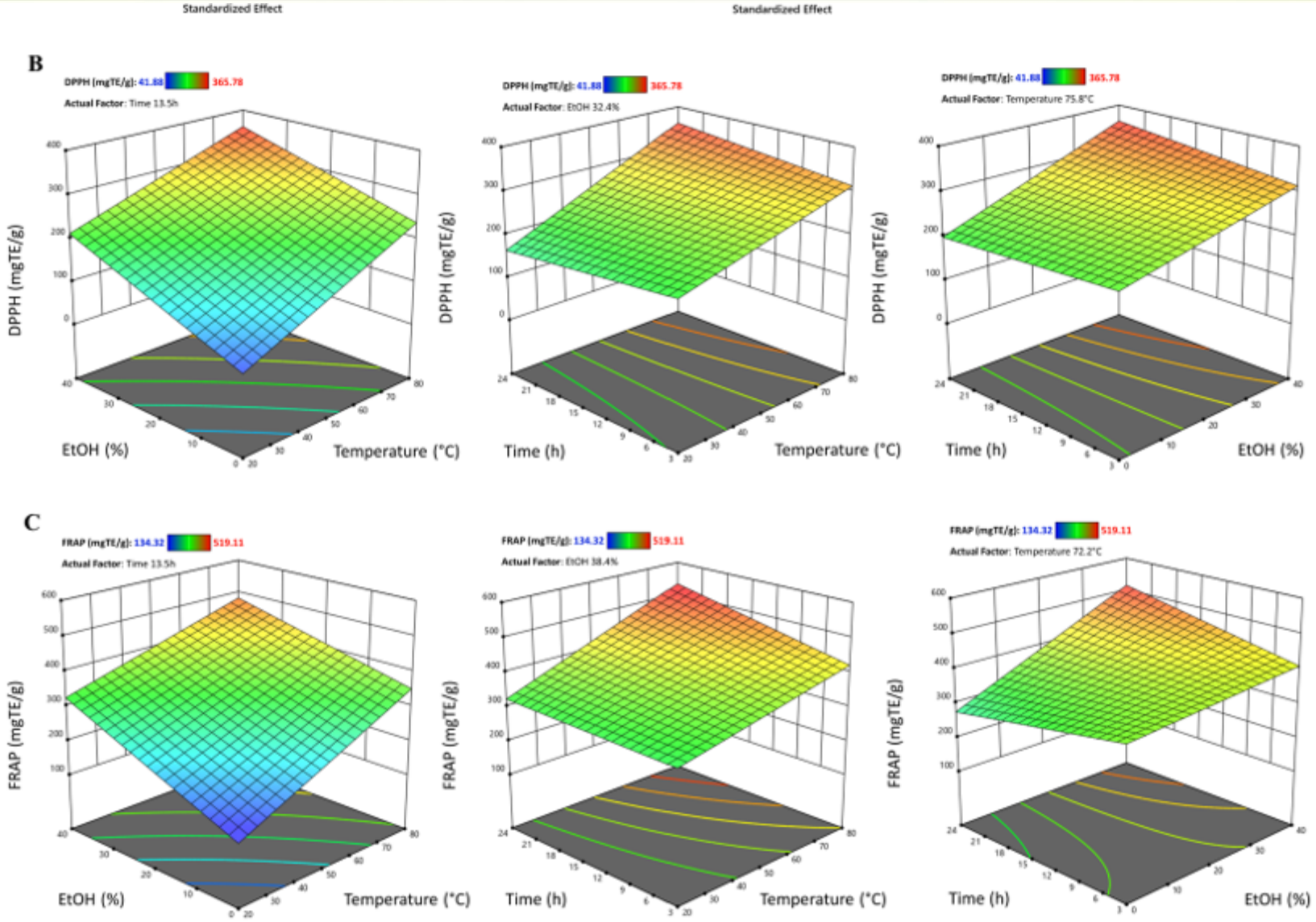
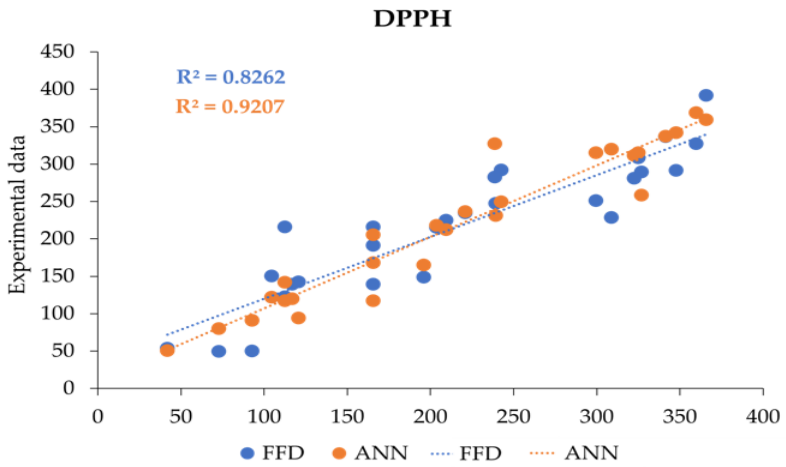
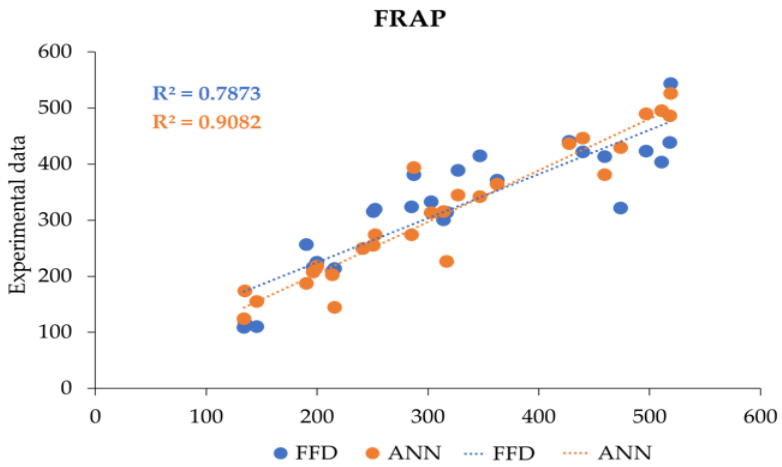


Figure 3. (**A**) Effects of independent variables (time, temperature, and solvent) on antioxidant activity; surface and contour plot of (**B**) 1,1-diphenyl-2-picryl hydrazyl (DPPH) scavenging activity and (**C**) Ferric Reducing Antioxidant Power (FRAP).

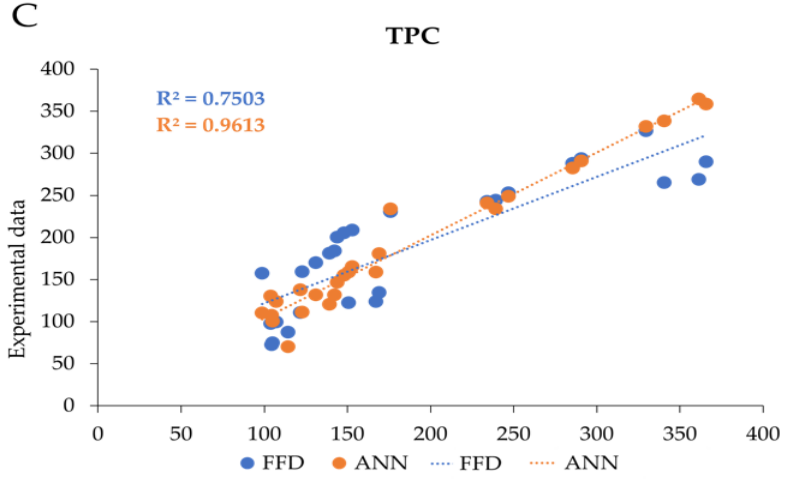
A


DPPH
R² = 0.8262
R² = 0.9207
Experimental data
0
50
100
150
200
250
300
350
400
450
FFD
ANN
FFD
ANN

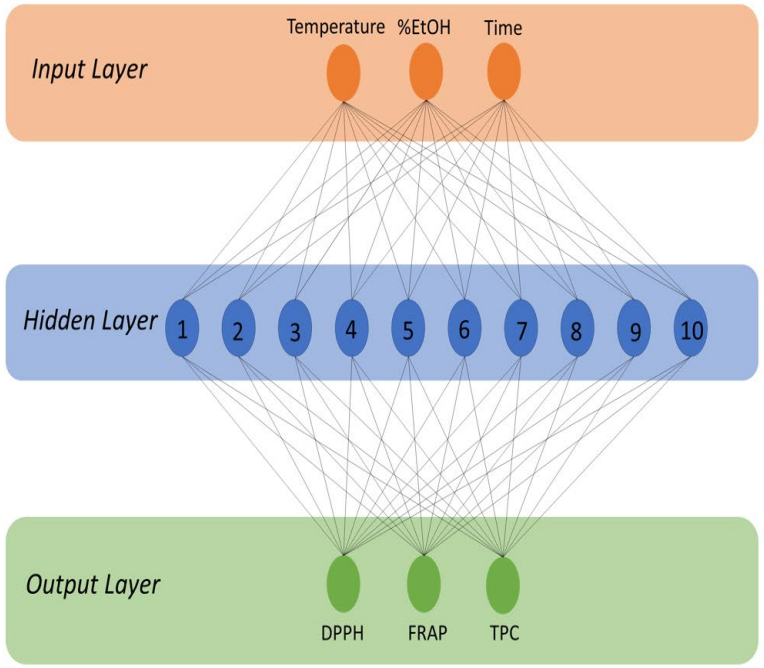
B


FRAP
R² = 0.7873
R² = 0.9082
Experimental data
0
100
200
300
400
500
600
FFD
ANN
FFD
ANN

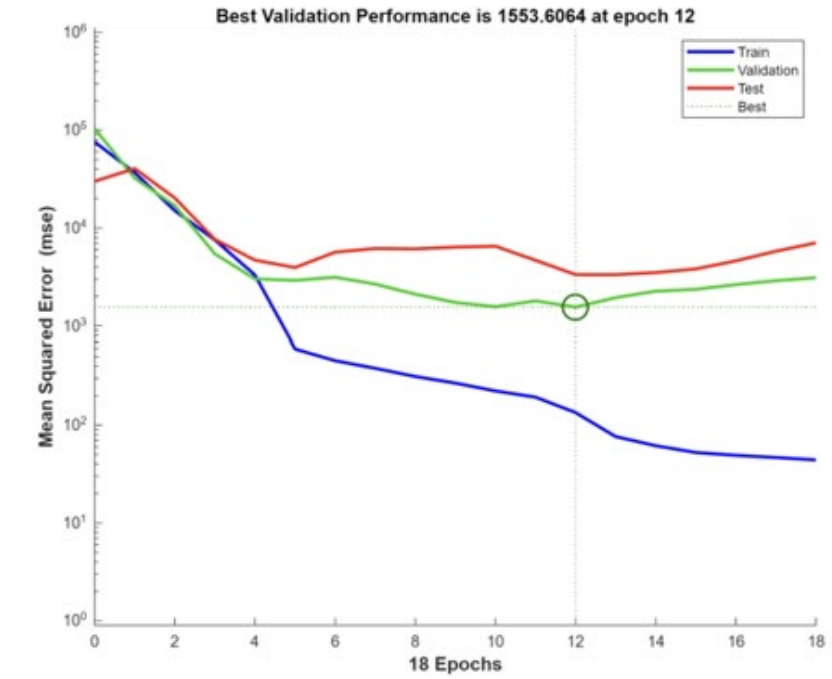
C


TPC
R² = 0.7503
R² = 0.9613
Experimental data
0
50
100
150
200
250
300
350
400
FFD
ANN
FFD
ANN

A

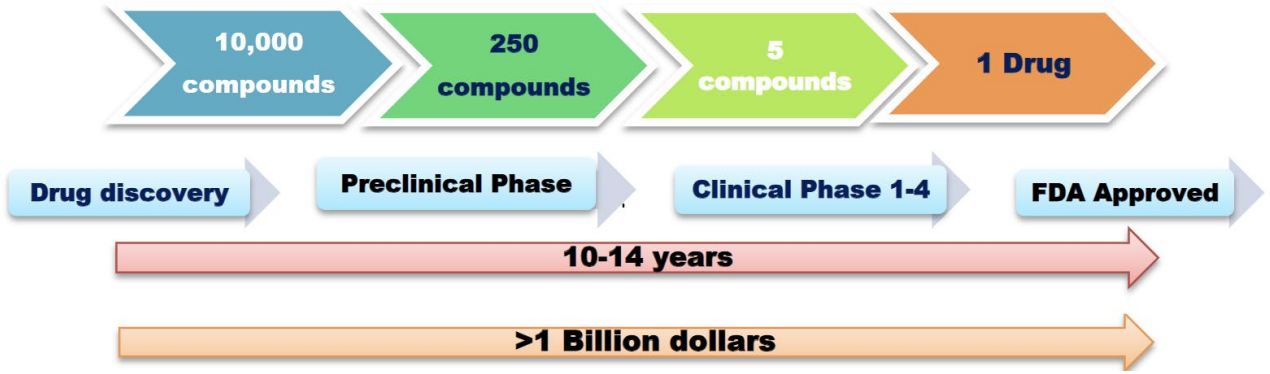

Temperature
%EtOH
Time
Input Layer
Hidden Layer
1
2
3
4
5
6
7
8
9
10
Output Layer
DPPH
FRAP
TPC

A

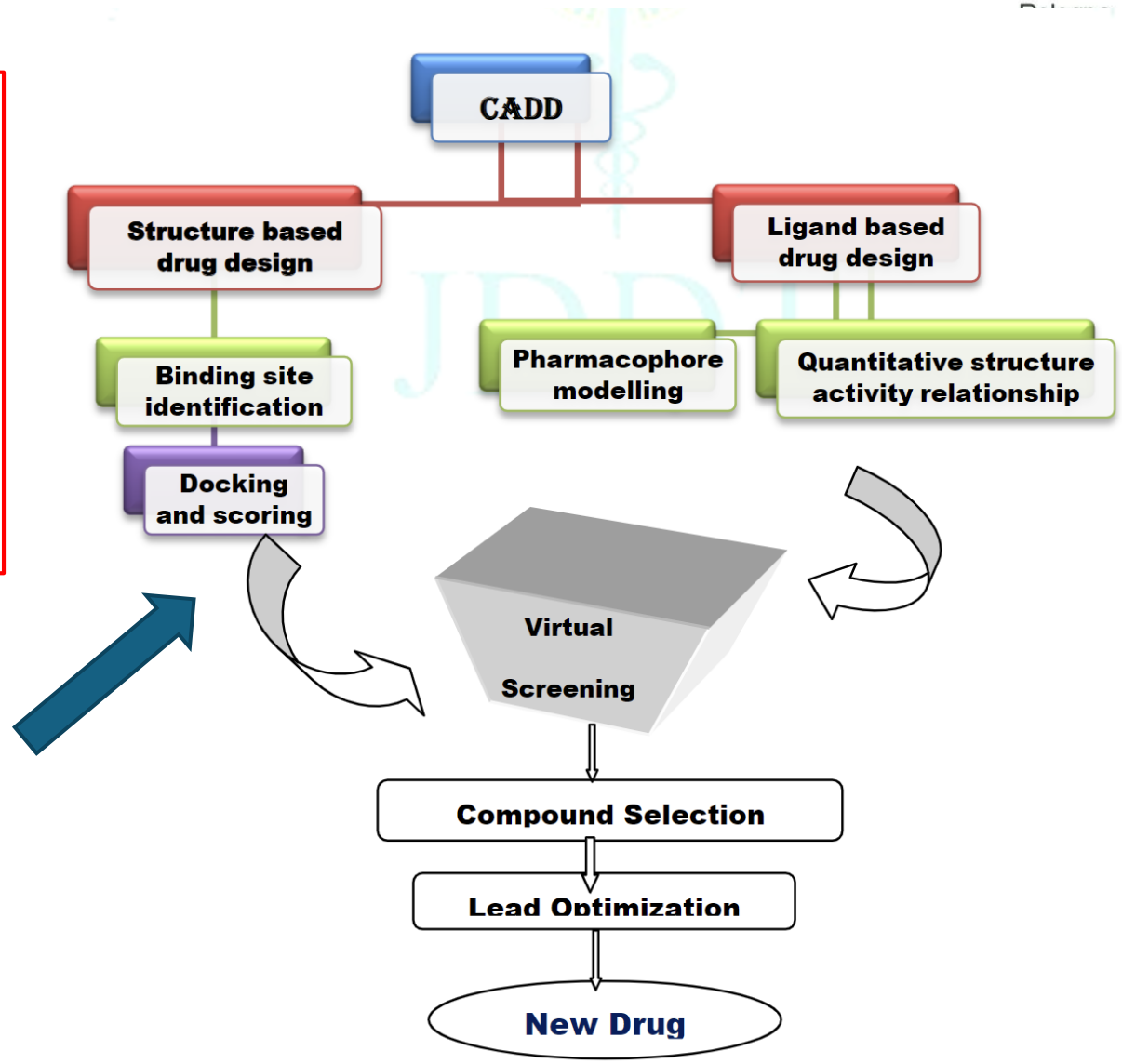

Best Validation Performance is 1553.6064 at epoch 12
Train
Validation
Test
Best
Mean Squared Error (mse)
18 Epochs

Il Drug Discovery nell'era IA

Processo tradizionale di scoperta e sviluppo dei farmaci

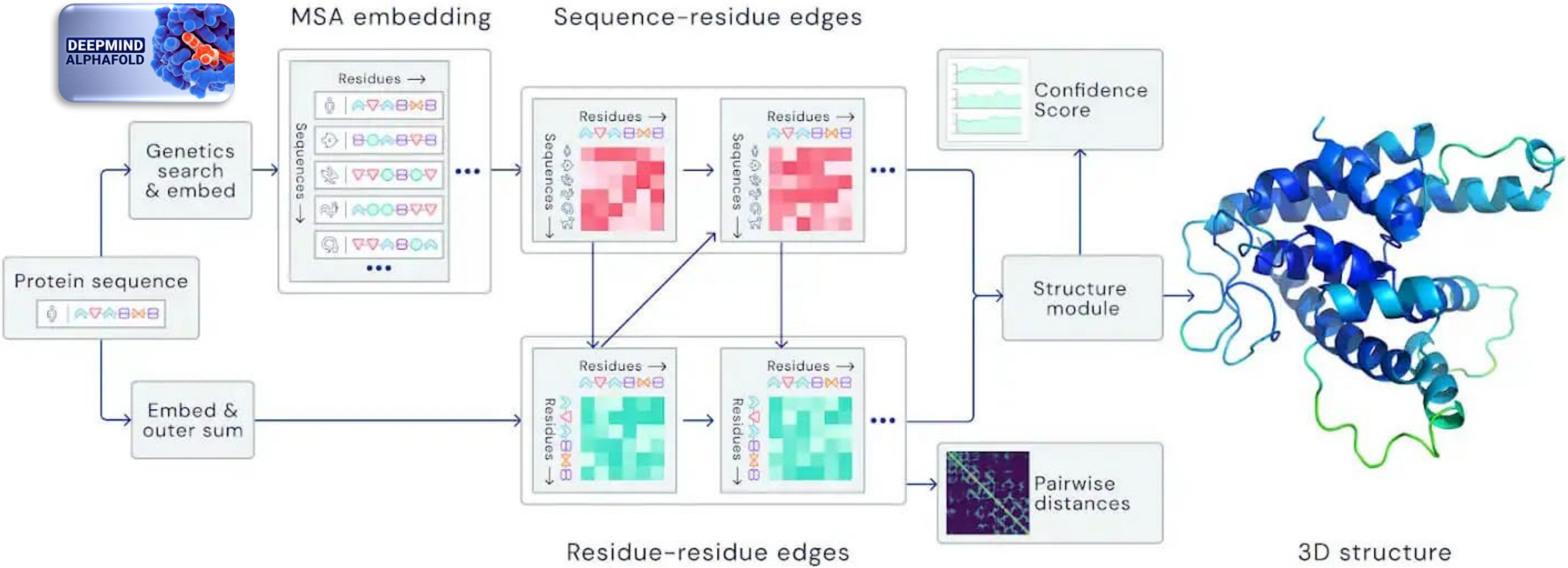


Il metodo CADD (Computer Aided Drug Design) è ampiamente utilizzato come approccio alla progettazione di nuovi farmaci. Si è visto che l'uso di approcci CADD può **ridurre i costi di scoperta e sviluppo dei farmaci fino al 50%**. Il CADD consiste nell'uso di un processo basato su un programma software per stabilire la relazione tra attività e struttura.



Surabhi, Surabhi, and B. K. Singh. "Computer aided drug design: an overview." Journal of Drug delivery and Therapeutics 8.5 (2018): 504-509.

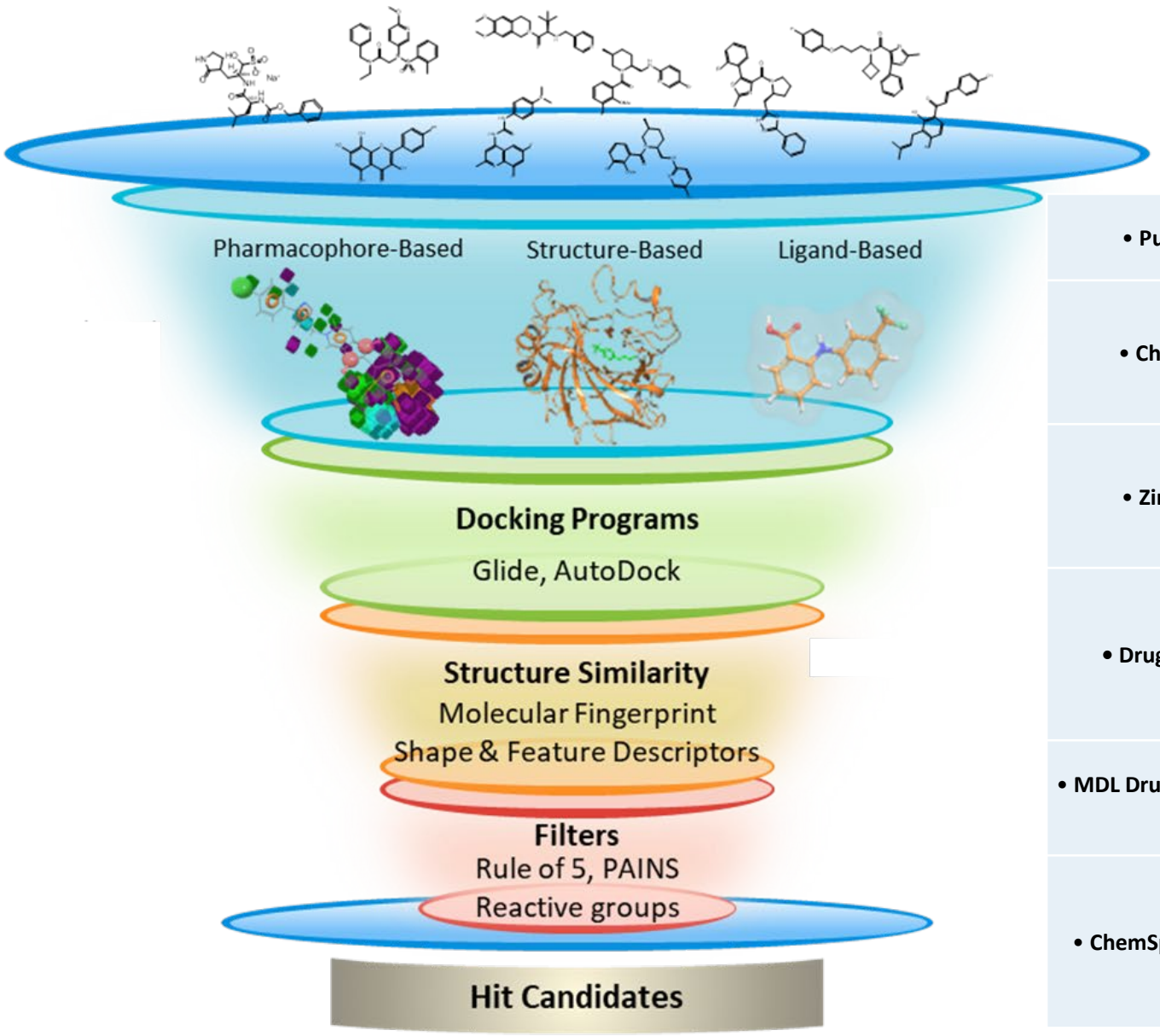
Homology modelling



Google DeepMind ha creato un sistema (AlphaFold) che prevede un addestramento della rete neurale su dati pubblici di circa 170.000 strutture proteiche insieme a grandi database contenenti sequenze proteiche di struttura sconosciuta.

Jumper, John, et al. "Highly accurate protein structure prediction with AlphaFold." nature 596.7873 (2021): 583-589.

Il *Drug Discovery*



Virtual Screening

• **PubChem** (Kim et al., 2016)	PubChem è un database pubblico che aggrega informazioni da database più piccoli e più specifici. Ha più di 97 milioni di composti disponibili.
• **ChEMBL** (Bento et al., 2014)	ChEMBL è un database di molecole bioattive con proprietà medicinali gestito dall'Istituto europeo di bioinformatica (EBI) dell'European Molecular Biology Laboratory (EMBL). Attualmente, contiene quasi 2,3 milioni di composti e 15,2 milioni di attività biologiche note.
• **Zinc** (Sterling e Irwin, 2015)	Zinc è un database gratuito di composti disponibili in commercio per VS. Zinco ha più di 230 milioni di composti disponibili in commercio in formato 3D. Zinco è gestito da Irwin e Shoichet Laboratories del Dipartimento di Chimica Farmaceutica presso l'Università della California, San Francisco (UCSF).
• **Drugbank** (Wishart et al., 2018)	DrugBank è un database che contiene informazioni molecolari complete sui farmaci, i loro meccanismi, le loro interazioni e i loro target. Il database contiene più di 11.900 voci di farmaci, tra cui circa 2.538 farmaci a piccole molecole approvati dalla FDA, 1.670 farmaci biotecnologici (proteine/peptidi) approvati dalla FDA, 129 nutraceutici e circa 6.000 farmaci sperimentali.
• **MDL Drug Data Report** (MDDR) (Sci Tegic Accelrys Inc, 2019)	MDDR è un database commerciale creato da database di brevetti, pubblicazioni e congressi. Contiene oltre 260.000 composti biologicamente rilevanti e circa 10.000 composti vengono aggiunti ogni anno.
• **ChemSpider** (Pence e Williams, 2010)	ChemSpider è un database di sostanze chimiche di proprietà della Royal Society of Chemistry. Contiene più di 71 milioni di strutture chimiche da oltre 250 fonti di dati. ChemSpider consente di scaricare fino a 1000 strutture al giorno. Per scaricare più strutture è necessario un contatto precedente e ChemSpider non è quindi un database totalmente gratuito.

Previsioni ADMET basate su intelligenza artificiale

COMPOSTI ANLIZZATI ED UTILIZZATI NEL VIRTUAL SCREENING

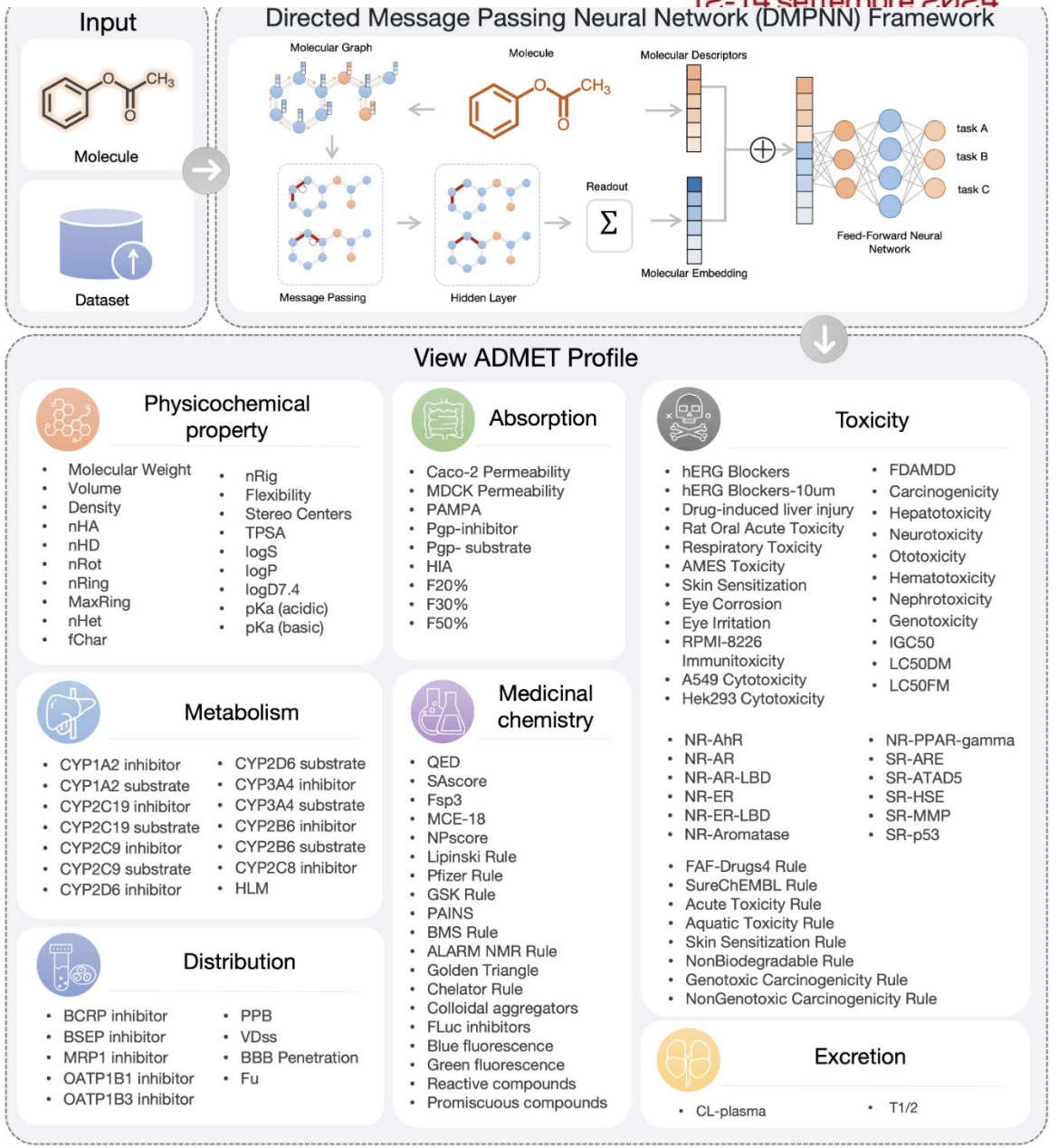
FILTRO REGOLA DI LIPINSKI

DOCKING SCREENING

COMPOSTI SELEZIONATI

Clinical Trial

ADMET AI algorithm



Generative AI will be designing new drugs all on its own in the near future

PUBLISHED SUN, MAY 5 2024•9:00 AM EDT | UPDATED MON, MAY 6 2024•1:59 PM EDT

Trevor Laurence Jockims

KEY POINTS

- Scientists at Eli Lilly have been surprised by novel design of molecules that AI has produced as part of hypothetical drug discovery research.
- A major precedent for AI-generated breakthroughs in biology was set in 2021 when Google's DeepMind AI, known for its creative thinking in realms ranging from the strategy game Go to music, video, and cloud computing, came up with a novel protein called AlphaFold.
- Within a few years, experts at Lilly and Nvidia say AI will not only think up new drugs, but ones that humans could not create.

Drug Discovery Today • Volume 29, Number 6 • June 2024 PERSPECTIVE

Feature

How successful are AI-discovered drugs in clinical trials? A first analysis and emerging lessons

Madura KP Jayatunga [1], Margaret Ayers [1], Lotte Bruens [2], Dhruv Jayanth [3], Christoph Meier [1,*]

[1] Boston Consulting Group, 80 Charlotte Street, London W1T 4DF, UK
[2] Boston Consulting Group, Gustav Mahlerlaan 40, 1082 MC Amsterdam, the Netherlands
[3] Boston Consulting Group, 466 Springfield Ave, Summit, NJ 07901, USA

Drug Discovery Today • Volume 29, Number 6 • June 2024 PERSPECTIVE

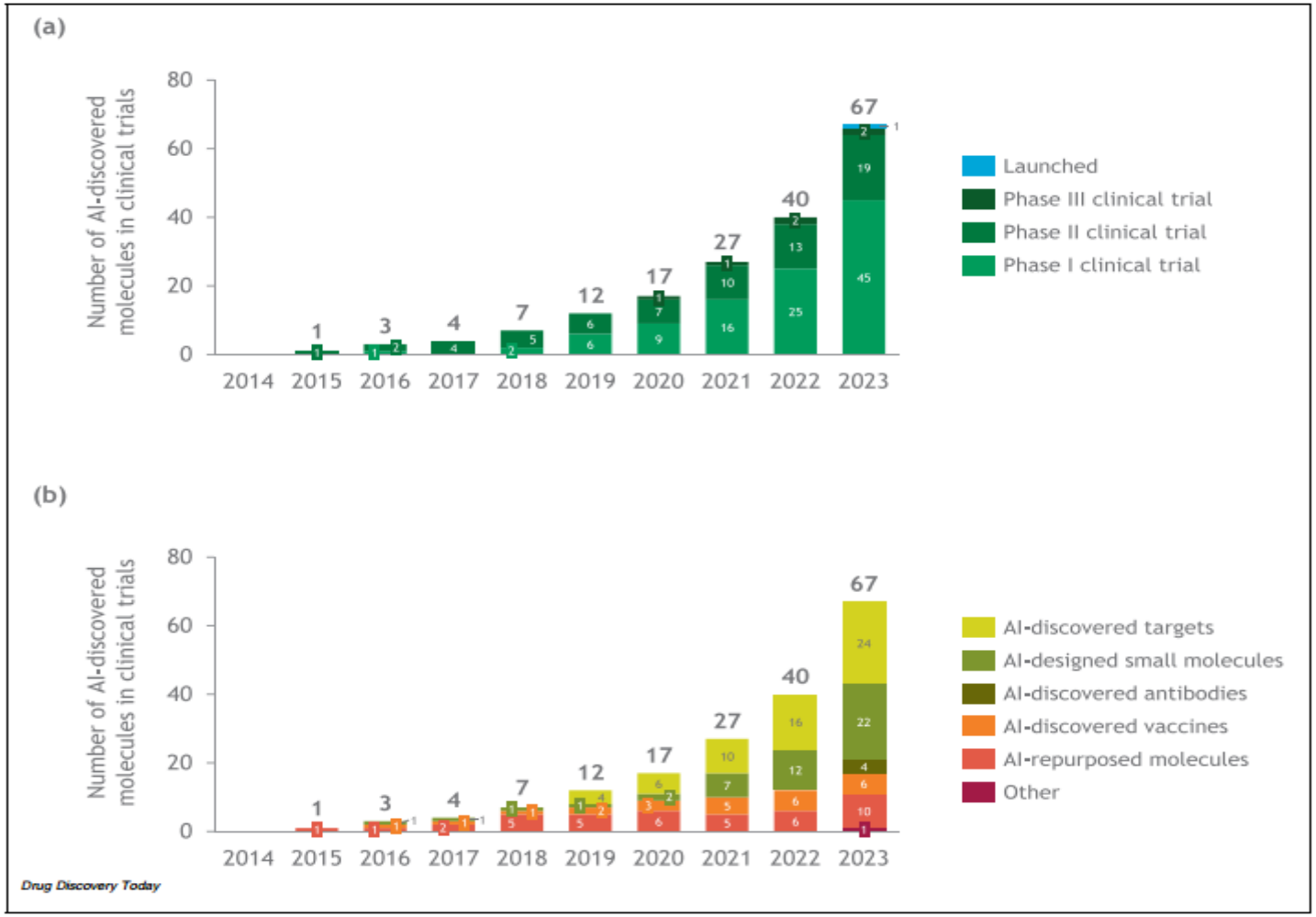


FIGURE 1
Number of molecules discovered by AI-first Biotechs that have entered clinical trials. The analysis includes molecules that were partnered with pharmaceutical companies and excludes COVID-19-related molecules. **(a)** AI-discovered molecules by clinical Phase. **(b)** AI-discovered molecules by mode-of-discovery.

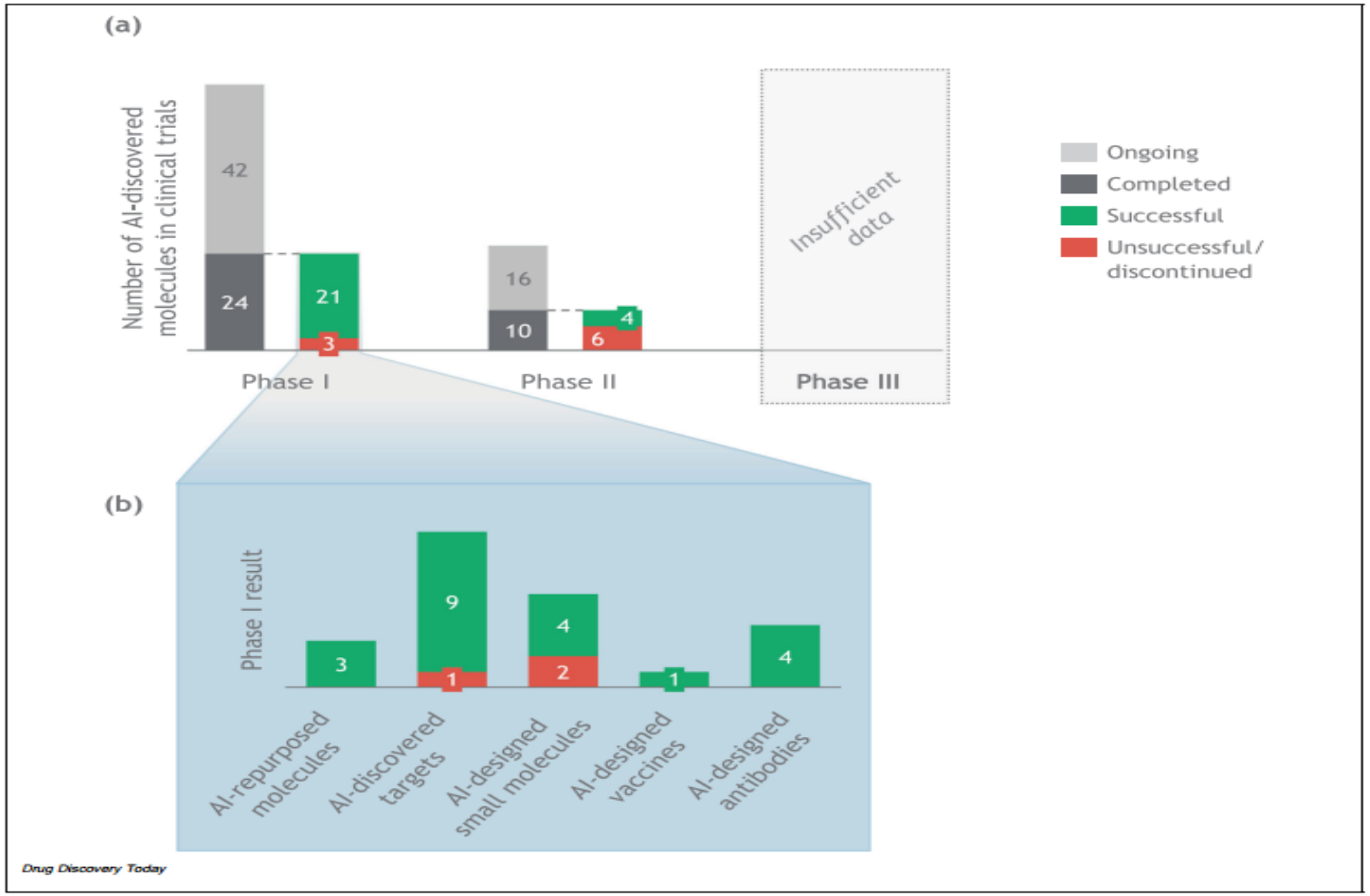


FIGURE 2

The success of AI-discovered molecules in clinical trials so far. The analysis includes molecules that were partnered with pharmaceutical companies and excludes COVID-19-related molecules. **(a)** Clinical success of AI-discovered molecules by clinical Phase. **(b)** AI-discovered molecules that have completed Phase I trial, by mode-of-discovery.

Take Home Messages

- L'elevata diversità chimica dei composti naturali è alla base della scoperta di nuove molecole farmacologicamente attive ed ad oggi è ancora inesplorata
- I metaboliti specializzati possono essere utilizzati come lead compounds per studi di virtual screening e portare allo sviluppo di nuove molecole sintetiche attive su specifici bersagli.
- l'applicazione dei ligand-based methods permettono di correlare la struttura chimica con un'attività biologica di interesse, di profilare le proprietà del composto nonché la sua possibilità di raggiungere un bersaglio.


L'INTELLIGENZA ARTIFICIALE
TI AFFASCINA O TI FA PAURA?

Grazie per l'Attenzione