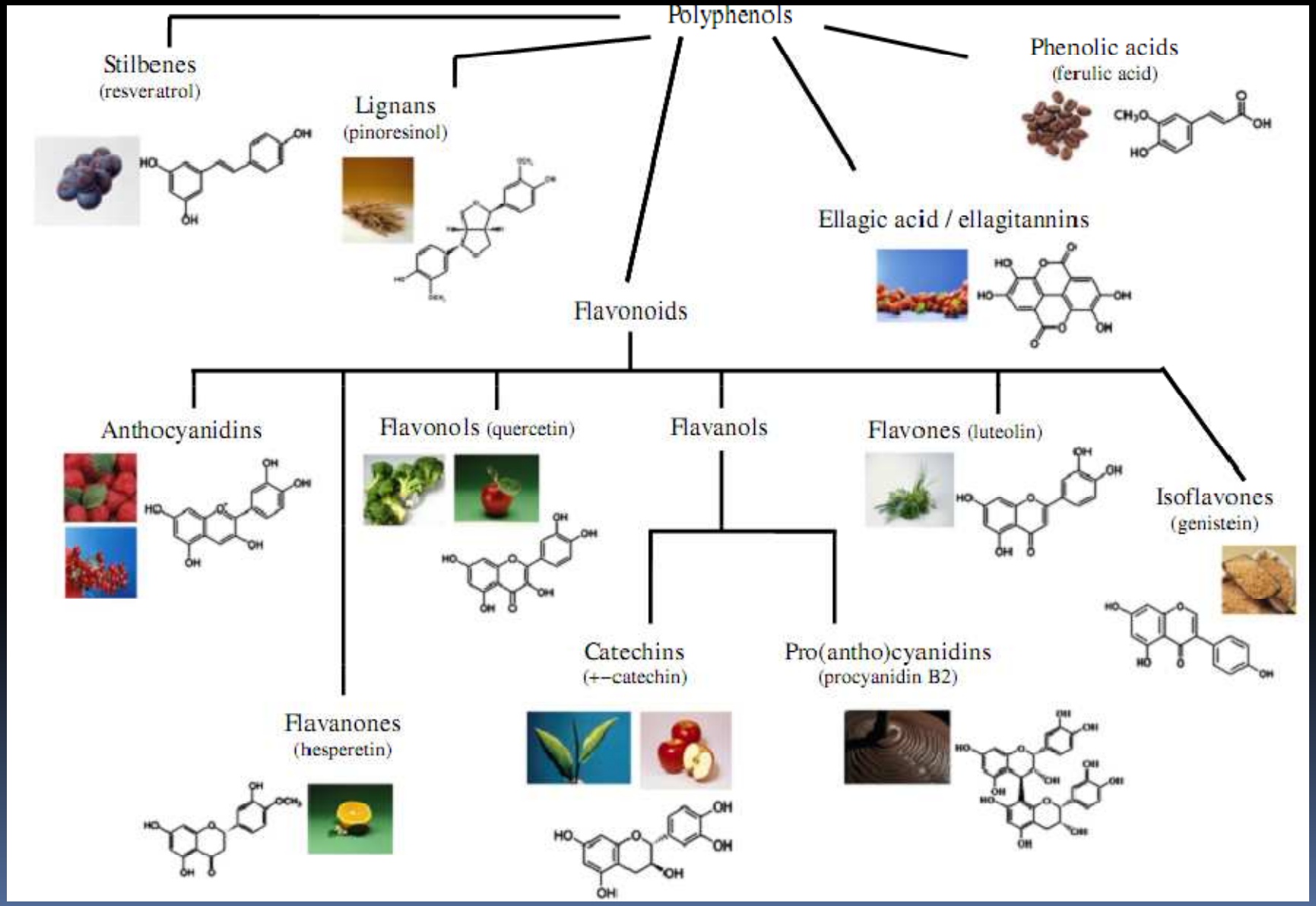
黄酮类化合物介导黑色素对UVR辐射损伤保护的应用

The protection of flavonoid-mediated melanocyte against UVR

清华大学深圳研究生院
史小军

- 一、黄酮类化合物简介
- 二、黑素细胞的生物活性
- 三、黄酮类成分介导黑素细胞对UVR的保护作用
- 四、应用展望

一、自然界中的黄酮类化合物



植物黄酮的生物活性：

Estrogen-like activity

Direct influence on extracellular matrix

Cardiovascular protective effect

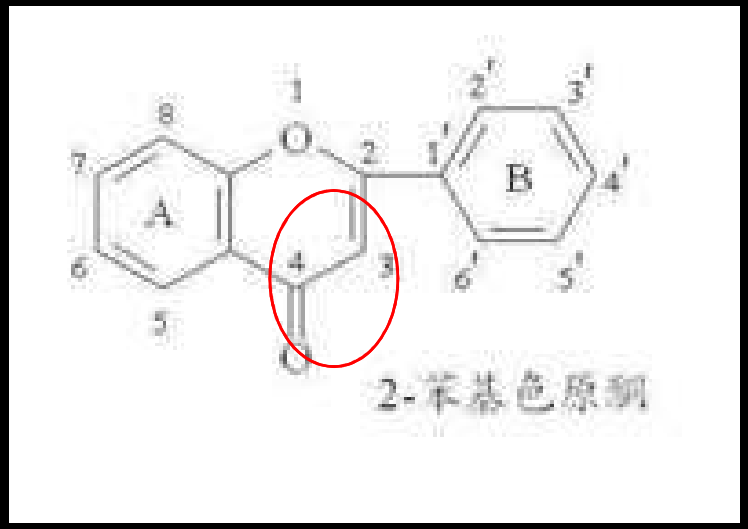
Anti-inflammatory and anti-allergic effect

Photoprotection

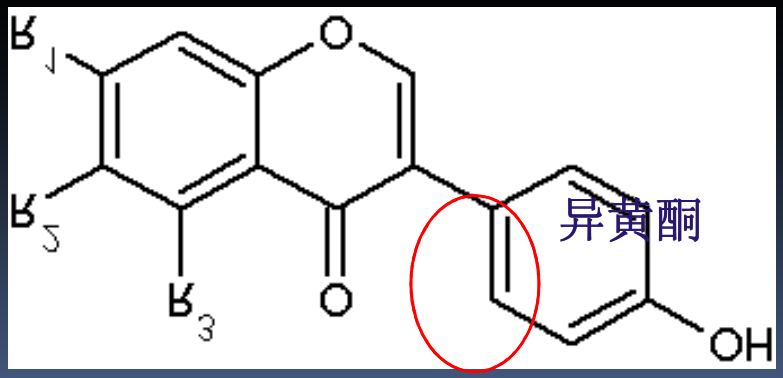
Anti-microbial activity

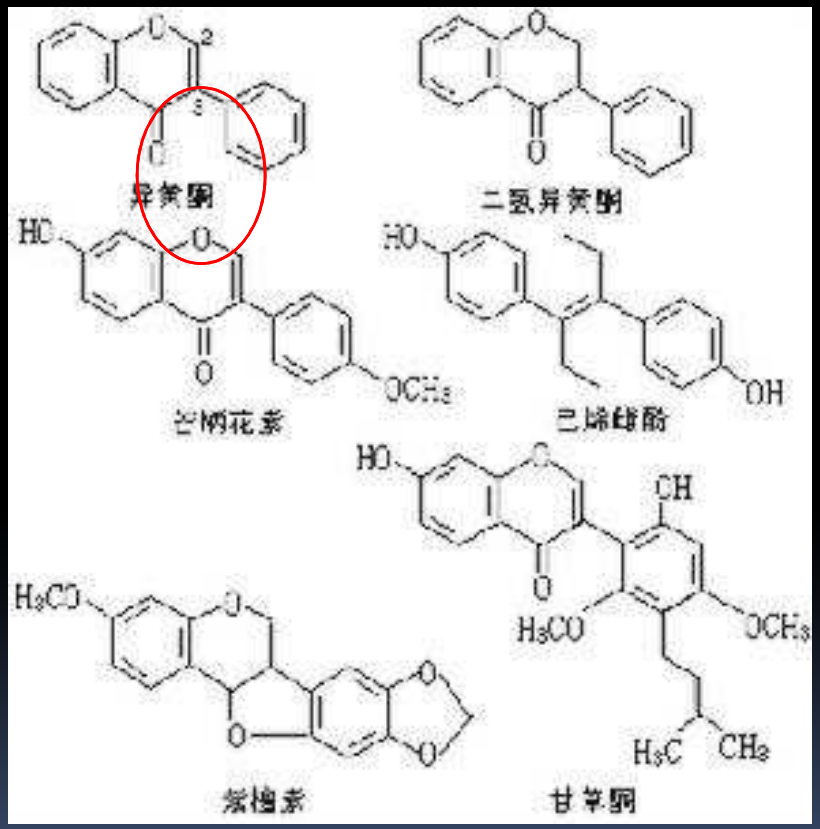
Anti-oxidative stress activity

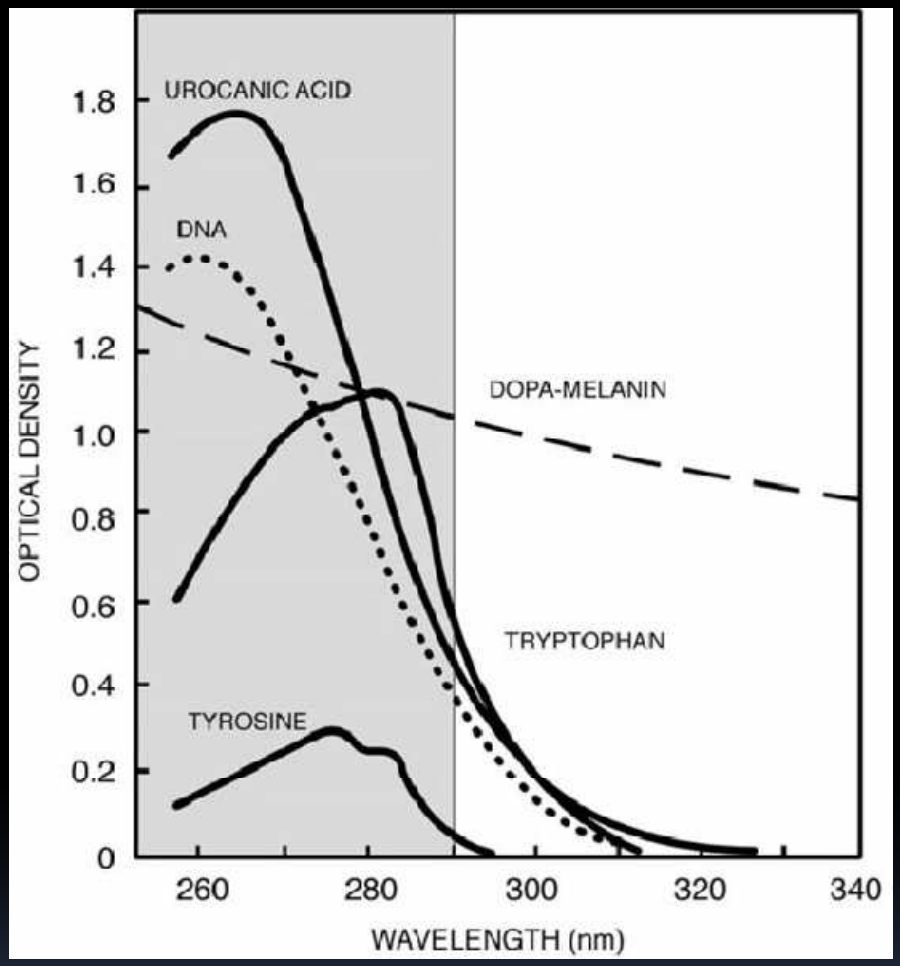
结构及代谢特点



黄酮







UVR absorption spectra of molecules important to UV-induced health effects

DOPA-melanin-synthetic model of eumelanin

自然生境中的次生代谢产物多样性

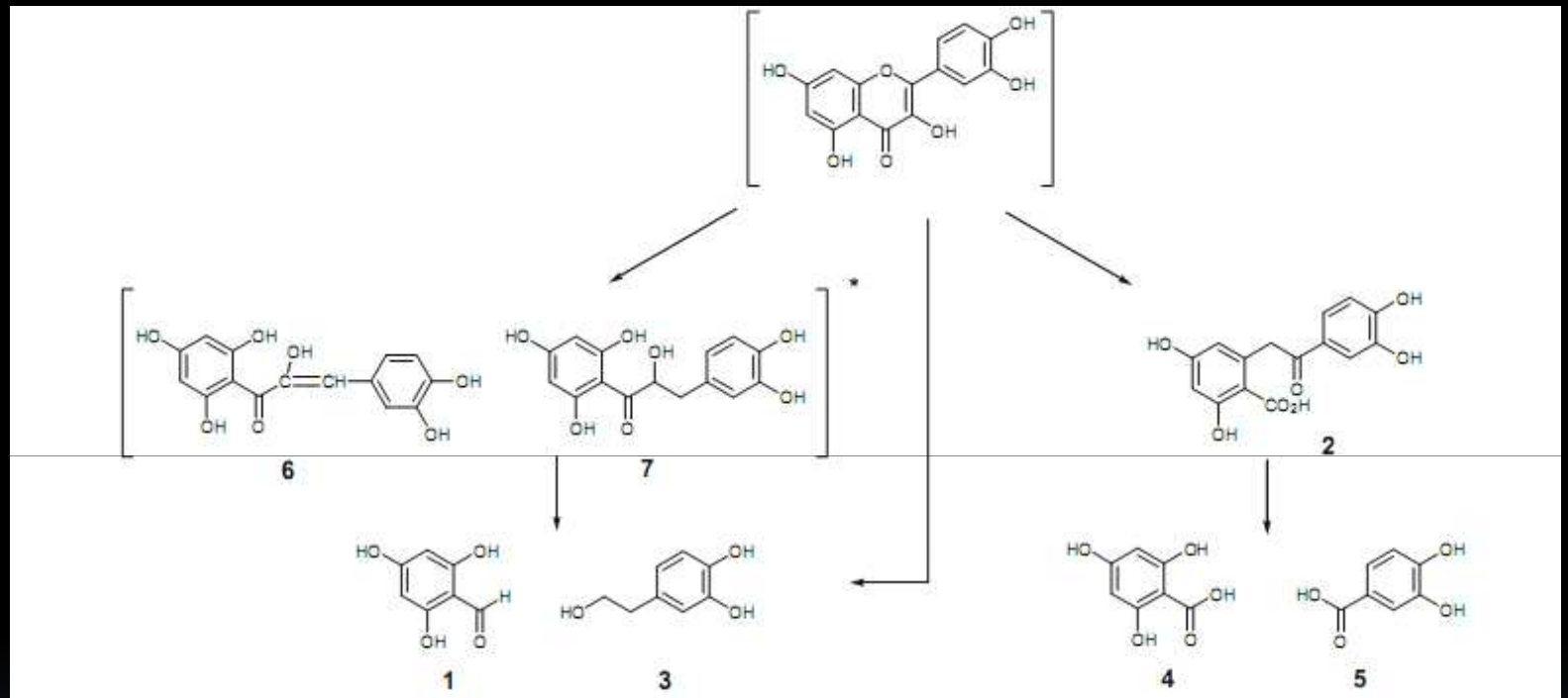


Fig. 7. Proposed reaction pathway for the UV radiation mediated decomposition of quercetin.

辐射强度、时间、温差等 独特气候条件， 生物抗逆性产生

过量紫外线照射

天然防晒剂：黄酮

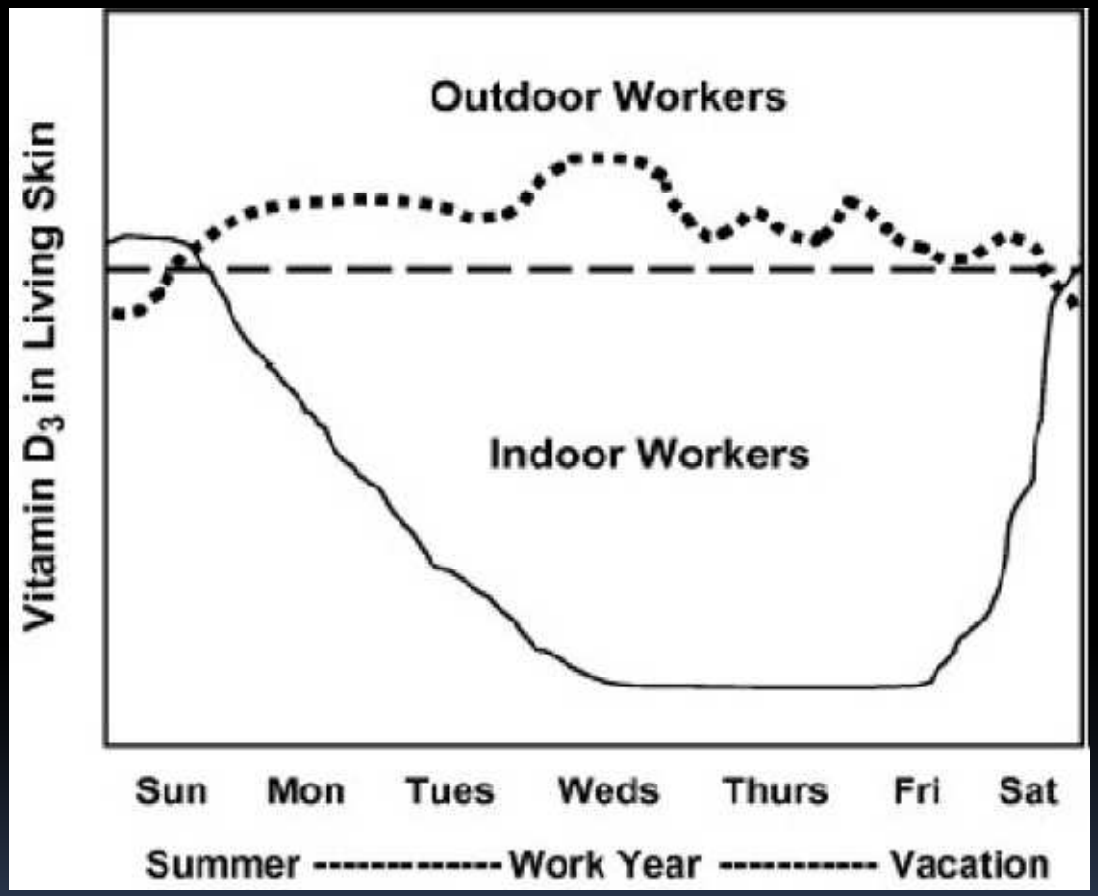
黄芩、芦丁 、光甘草素.....

- 光酶性DNA 修复
- 紫外线修复酶系统
- 核酸切除修复系统

二元切割由UvrA，UvrB 和UvrC三种蛋白来完成，而在人体细胞中，需要6 种修复因子中的14~15 种多肽来完成此项任务\

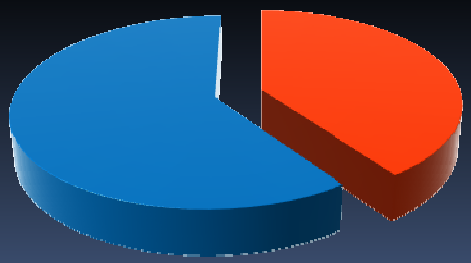
- 其他修复机制

SOS 修复、二聚体旁路、重组修复、细胞周期检查点、凋亡等修复方式在许多生物中都是有效的DNA 修复方式

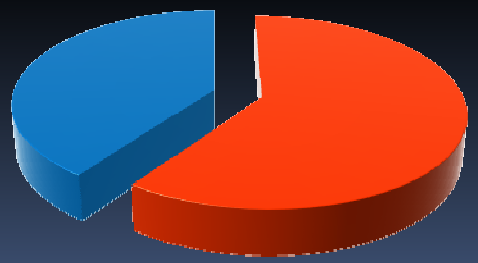

Outdoor Workers
Indoor Workers
Vitamin D3 in Living Skin
Sun
Mon
Tues
Weds
Thurs
Fri
Sat
Summer ---------- Work Year ---------- Vacation

古老的天然化妆品 → 化学合成化妆品 → 现代天然化妆品

欧洲



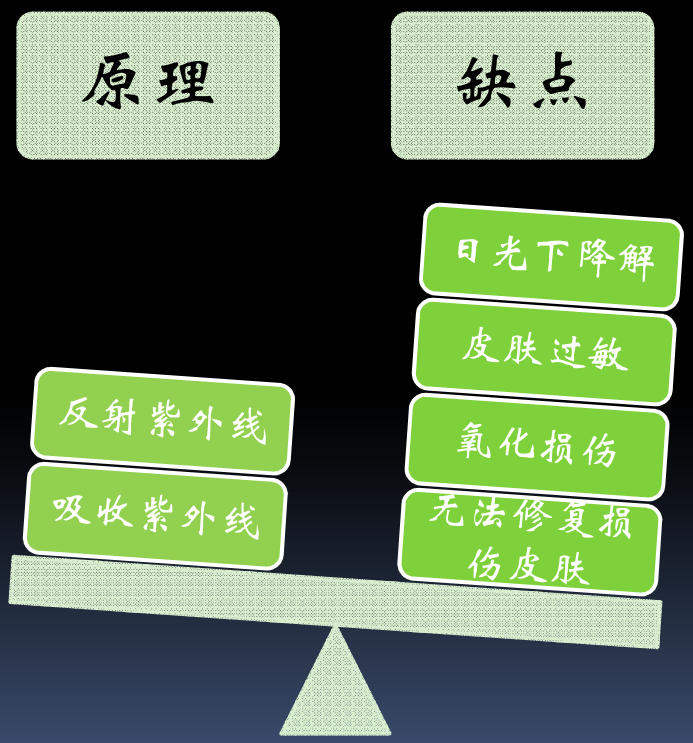
日本



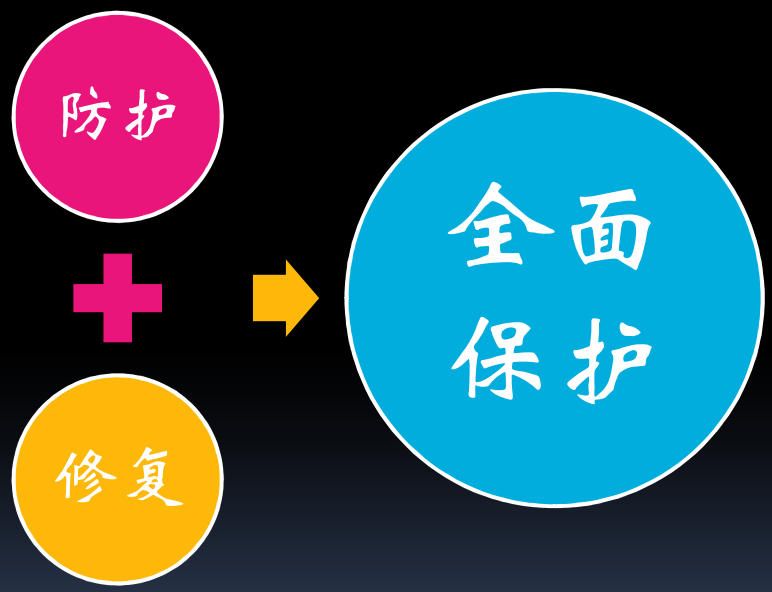
天然化妆品

合成化妆品

传统防晒产品



天然防晒产品

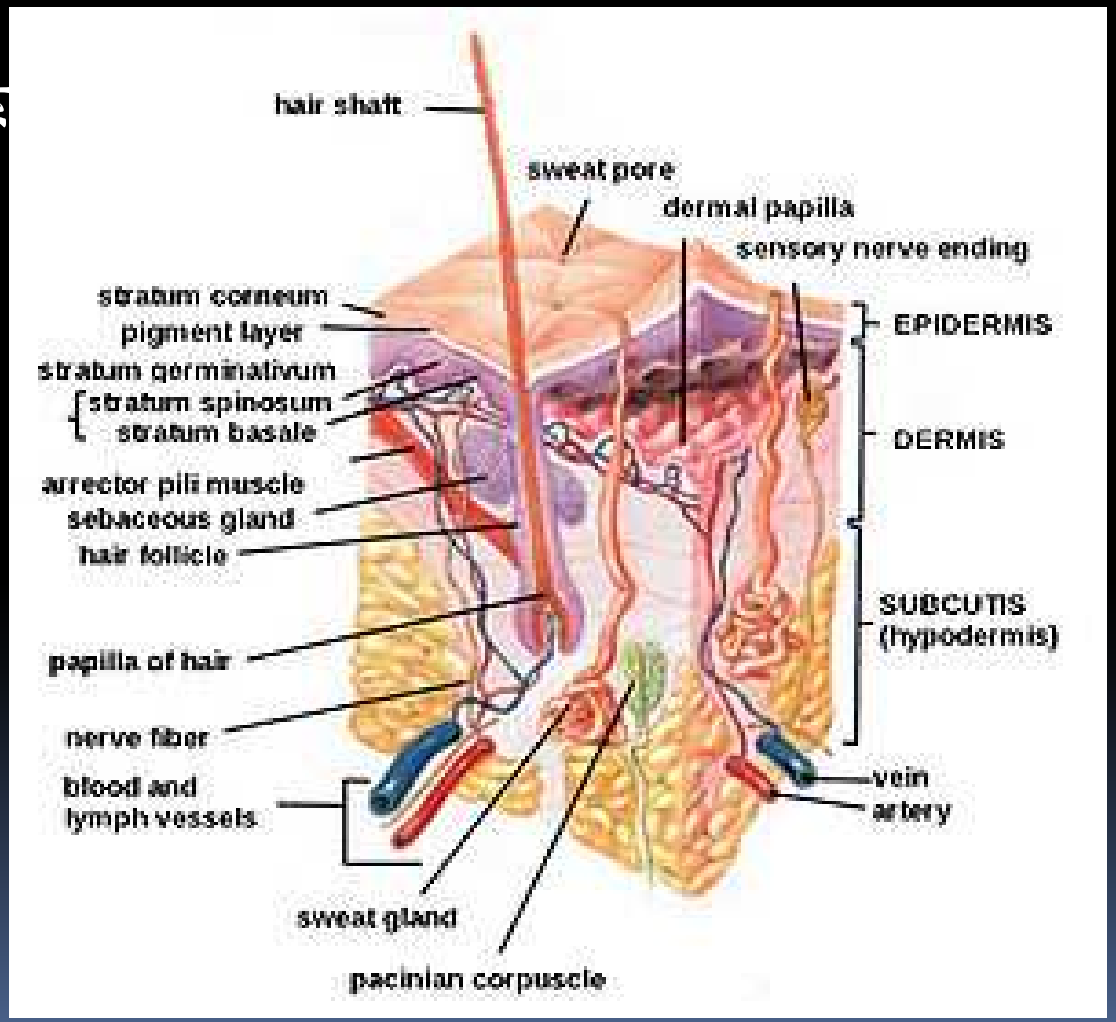


Cosmetic ingredients and cancer risk

Cosmetic substance	Risk
DEA (diethanolamine)二乙醇胺） TEA (triethanolamine) （三乙醇胺）	can result in formation of carcinogenic nitrosamines
Bronopol (2-bromo-2-nitropropane-1,3-diol) 溴硝醇	may break down into formaldehyde and also cause the formation of nitrosamines
1,2-Dioxane in surfactants/detergents	contaminated with carcinogenic 1,4-dioxane
Artificial colours (as Blue 1 and Green 3)	Carcinogenic
Hair dyes	dark colours ingredients are carcinogenic
Cosmetic lanolin Talc Carcinogenic	can be contaminated with carcinogenic pesticides such as DDT, dieldrin, and lindane, in addition to other neurotoxic pesticides
Silica	may be contaminated with carcinogenic crystalline quartz

二、黑素细胞及生物活性

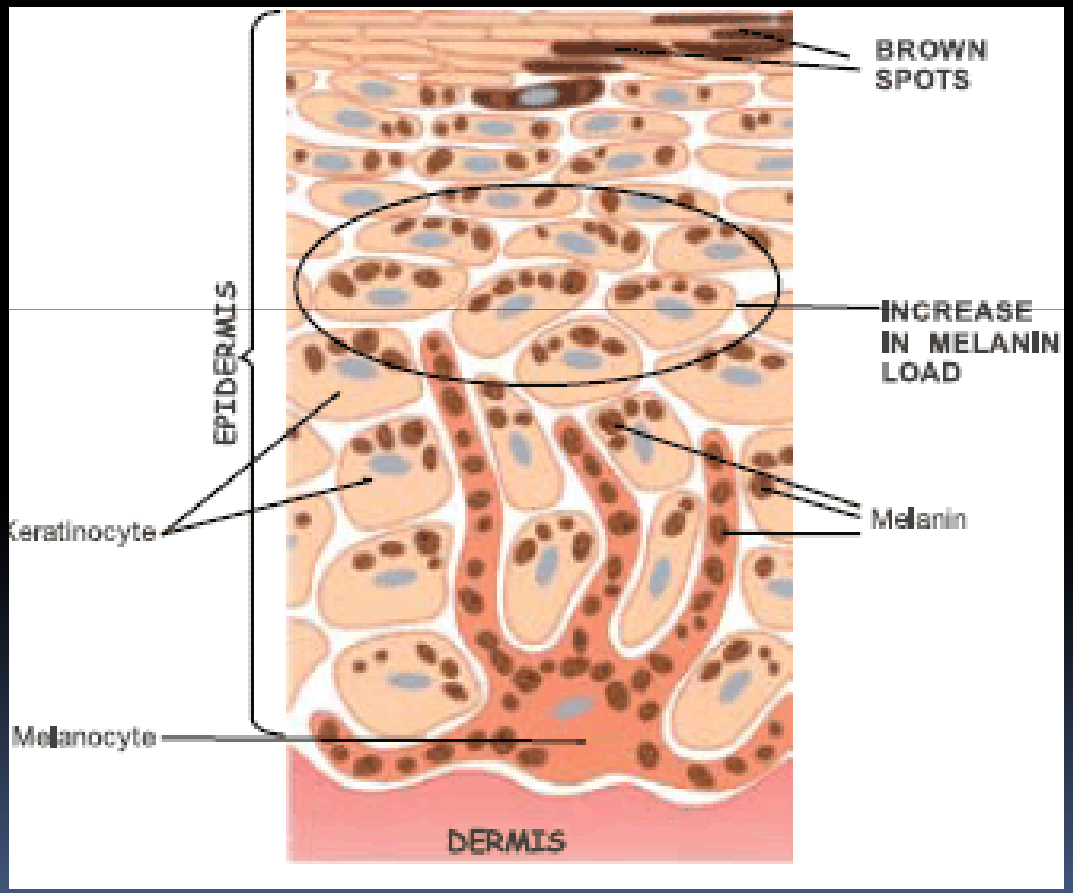
- 皮肤中的黑色素



Epidermis:表皮 Dermis:真皮

皮肤中的黑色素

表皮中：
Melanocytes:Keratinocytes
≈1:36
构成一个表皮单元



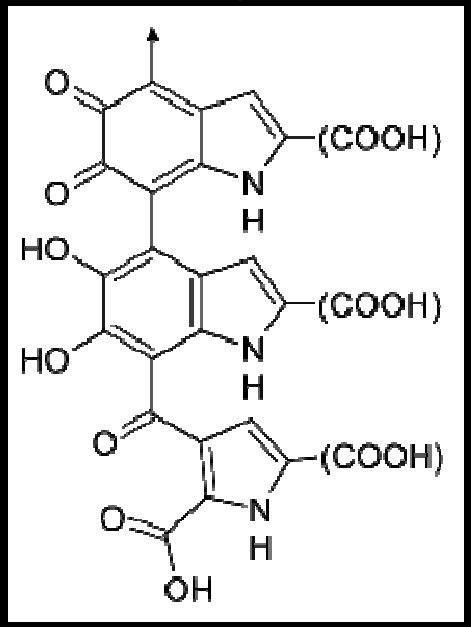
Melanocyte:黑色素细胞 Keratinocyte:角质形成细胞 Melanin:黑色素

黑色素细胞的来源及结构基础

- 黑素细胞起源于胚胎神经嵴，具有树状突起，属于腺细胞。黑素细胞可以产生及分泌黑色素。
- Melanosome即黑素小体，是黑素细胞特有细胞器，可产生黑色素，并将其运送至角质形成细胞。

Melanosome:黑素小体

黑色素的合成



Part of the structural formula of the **eumelanin**. -COOH can be -COOH or -H, or very rarely other substituents. The arrow denotes where the polymer continues.

- **Eumelanin真黑素**

  黑色或棕色

  来自椭圆黑色小体

- **Pheomelanin类黑素**

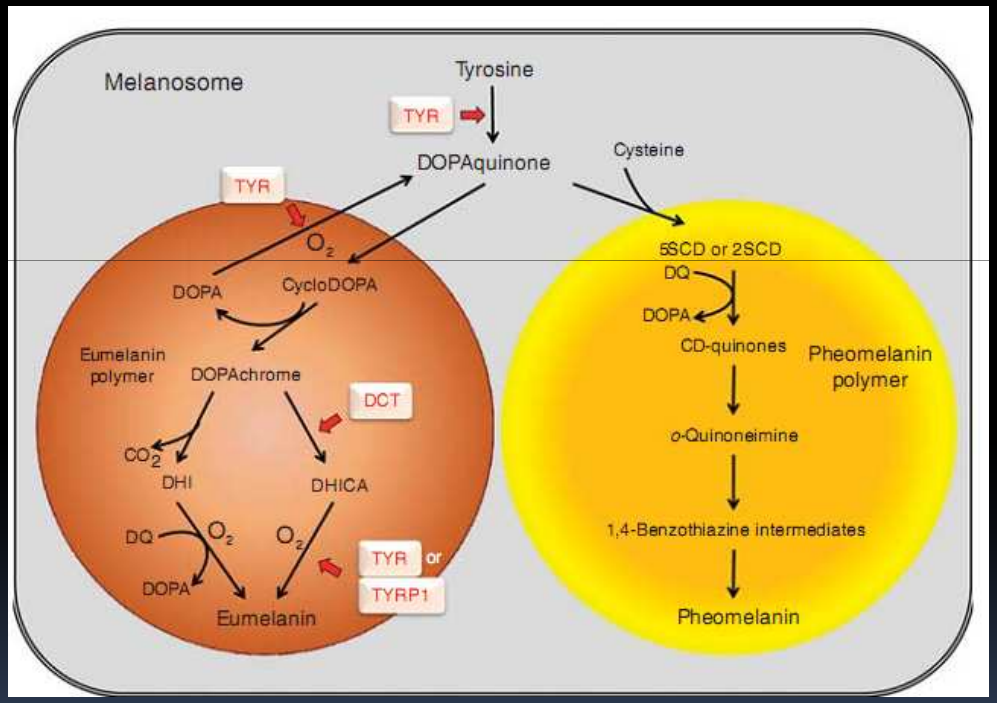
  呈红色至粉色

  来自较小的圆形黑色小体

- *Neuromelanin神经黑素

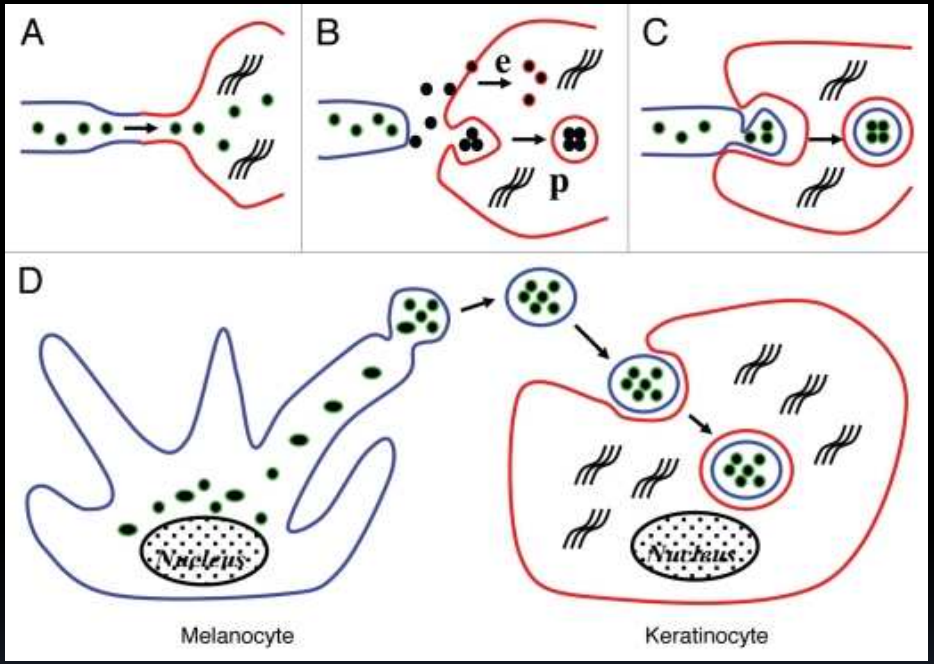
  人神经核在出生时无色，成熟后变黑

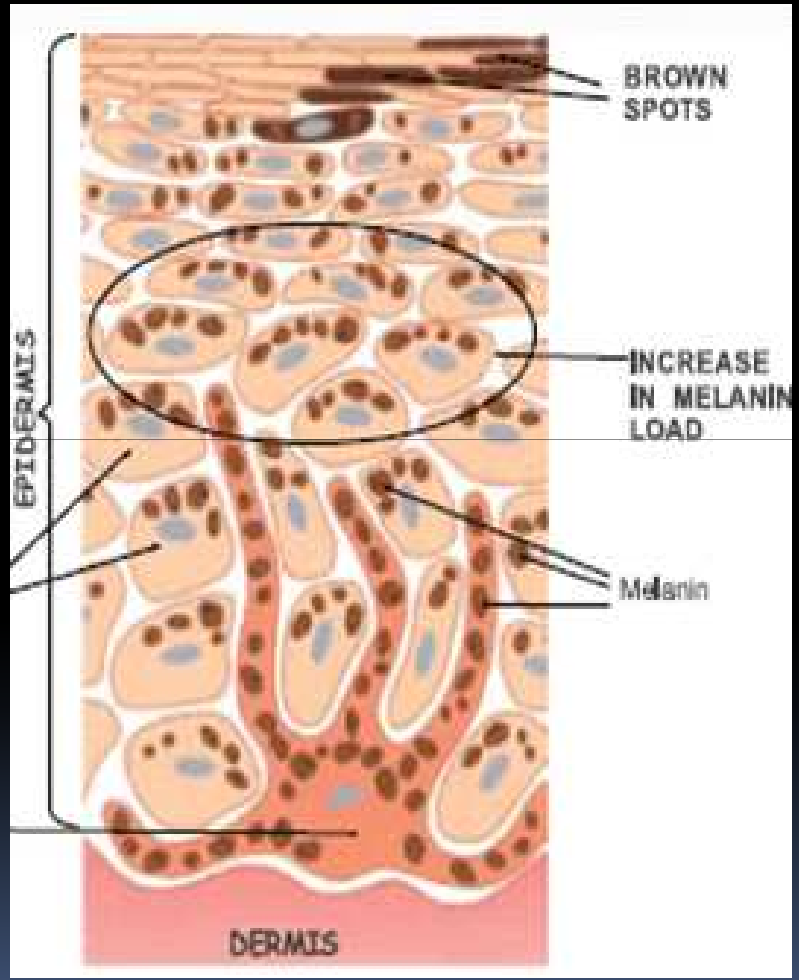
黑色素的合成



- 多步骤酶促反应：
  - ✓ 酪氨酸酶tyrosinase, TYR
  - ✓ DCT即TRP2
  - ✓ TYRP1即TRP1

黑色素的分泌


A
B
e
p
C
D
Nucleus
Nucleus
Melanocyte
Keratinocyte


BROWN SPOTS
INCREASE IN MELANIN LOAD
EPIDERMIS
Melanin
DERMIS

A-MSH

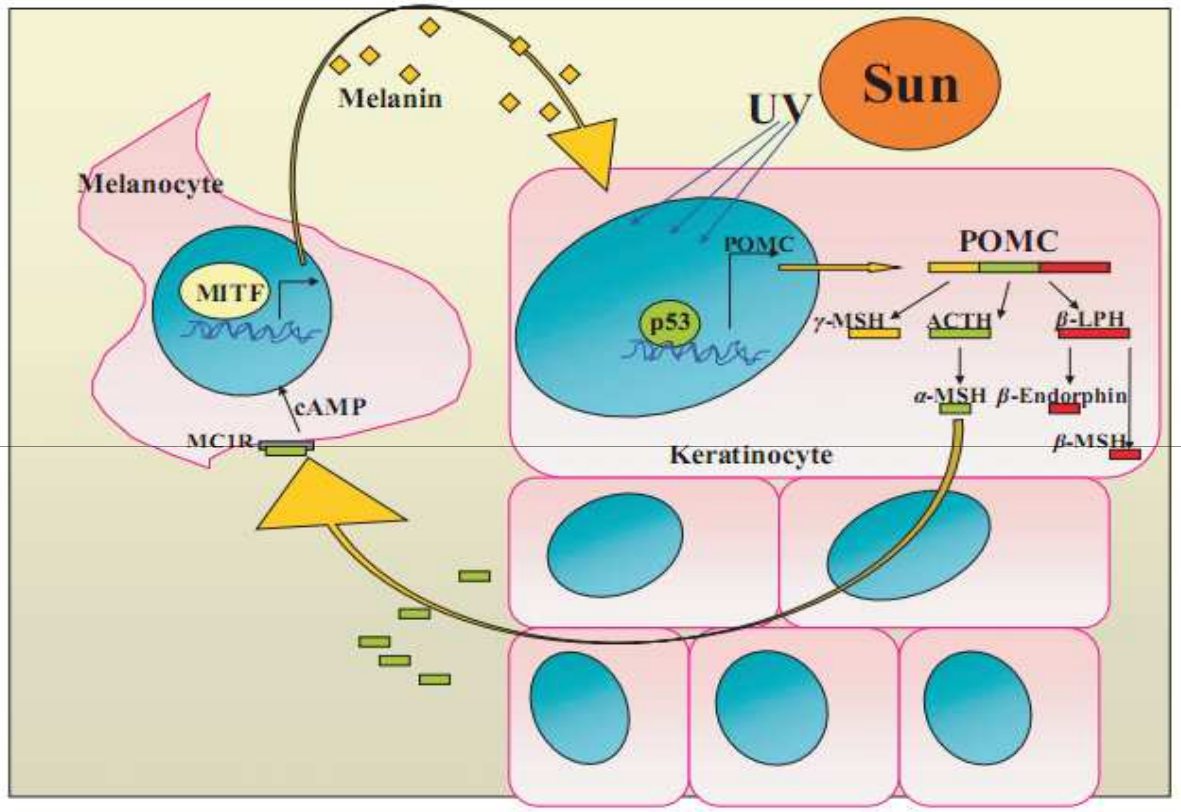
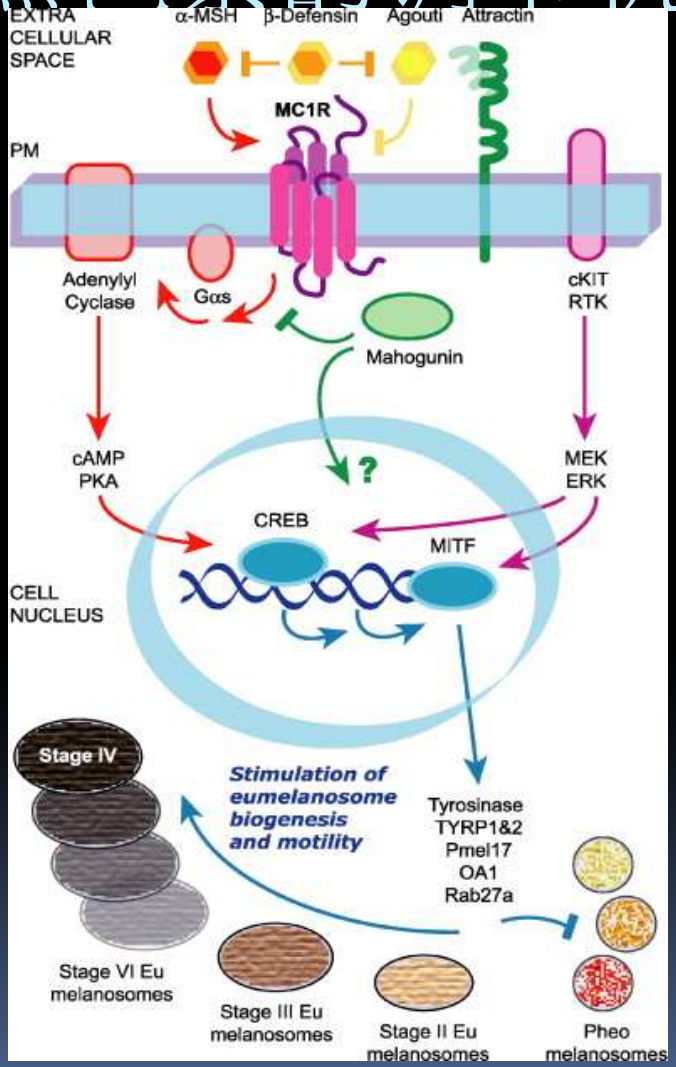
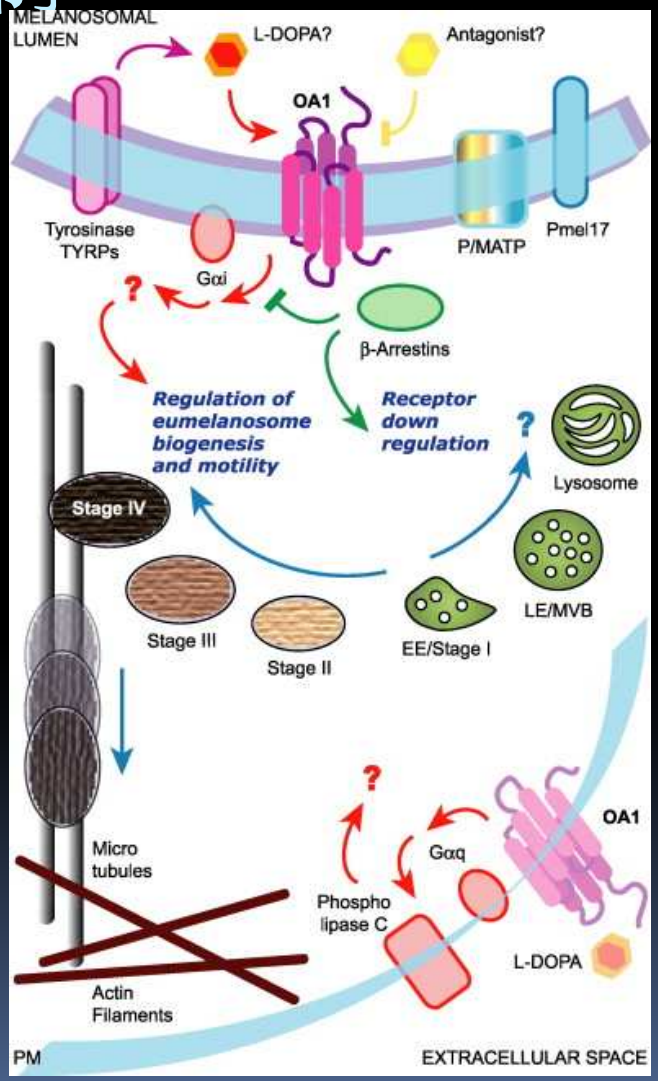


Figure 2. The UV-pigmentation (tanning) pathway. UV induces DNA damage, which leads to activation/stabilization of p53. In turn, p53 stimulates transcriptional upregulation of the proopiomelanocortin (POMC) gene, which is post-translationally processed for gamma-melanocyte-stimulating hormone (γMSH), adrenocorticotrophic hormone (ACTH), beta-lipotropic hormone (β-LPH), α-melanocyte-stimulating hormone (αMSH), b-endorphin, and β-melanocyte-stimulating hormone (β-MSH). Secreted αMSH binds and activates its receptor on melanocytes (melanocortin 1 receptor (MC1R)), leading to upregulation of cAMP that in turn leads to stimulated expression of MITF, which then transcriptionally activates expression of the enzymatic machinery leading to synthesis, maturation, and transport of melanin-containing vesicles called melanosomes to the overlying epidermal (or hair follicle) keratinocytes.

黑色素的调节机制


EXTRA CELLULAR SPACE
α-MSH
β-Defensin
Agouti
Attractin
MC1R
PM
Adenylyl Cyclase
Gαs
cKIT RTK
Mahogunin
cAMP PKA
MEK ERK
CREB
MITF
CELL NUCLEUS
Stage IV
Stimulation of eumelanosome biogenesis and motility
Tyrosinase TYRP1&2 Pmel17 OA1 Rab27a
Stage VI Eu melanosomes
Stage III Eu melanosomes
Stage II Eu melanosomes
Pheo melanosomes


MELANOSOMAL LUMEN
L-DOPA?
Antagonist?
OA1
Tyrosinase TYRPs
P/MATP
Pmel17
Gαi
β-Arrestins
Regulation of eumelanosome biogenesis and motility
Receptor down regulation
Lysosome
Stage IV
LE/MVB
Stage III
Stage II
EE/Stage I
Micro tubules
Actin Filaments
Gαq
Phospho lipase C
OA1
L-DOPA
PM
EXTRACELLULAR SPACE

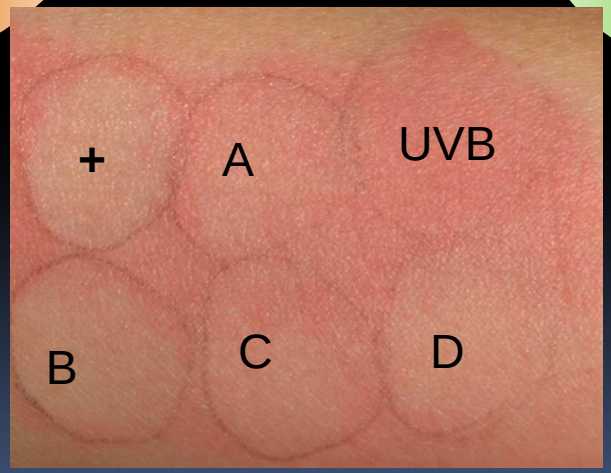
不同因素对黑素细胞的影响

黑素细胞在发育过程中，受内外因素的影响其生长、分化、增殖、迁移、凋亡、黑素合成等过程中某一个或几个环节出现异常，将导致黑色素形成和沉着异常，发生色素障碍性疾病。各种不同的内外因素通过不同的环节对黑素细胞的功能产生一定影响。

三、黄酮类成分介导黑素细胞对UVR的保护作用

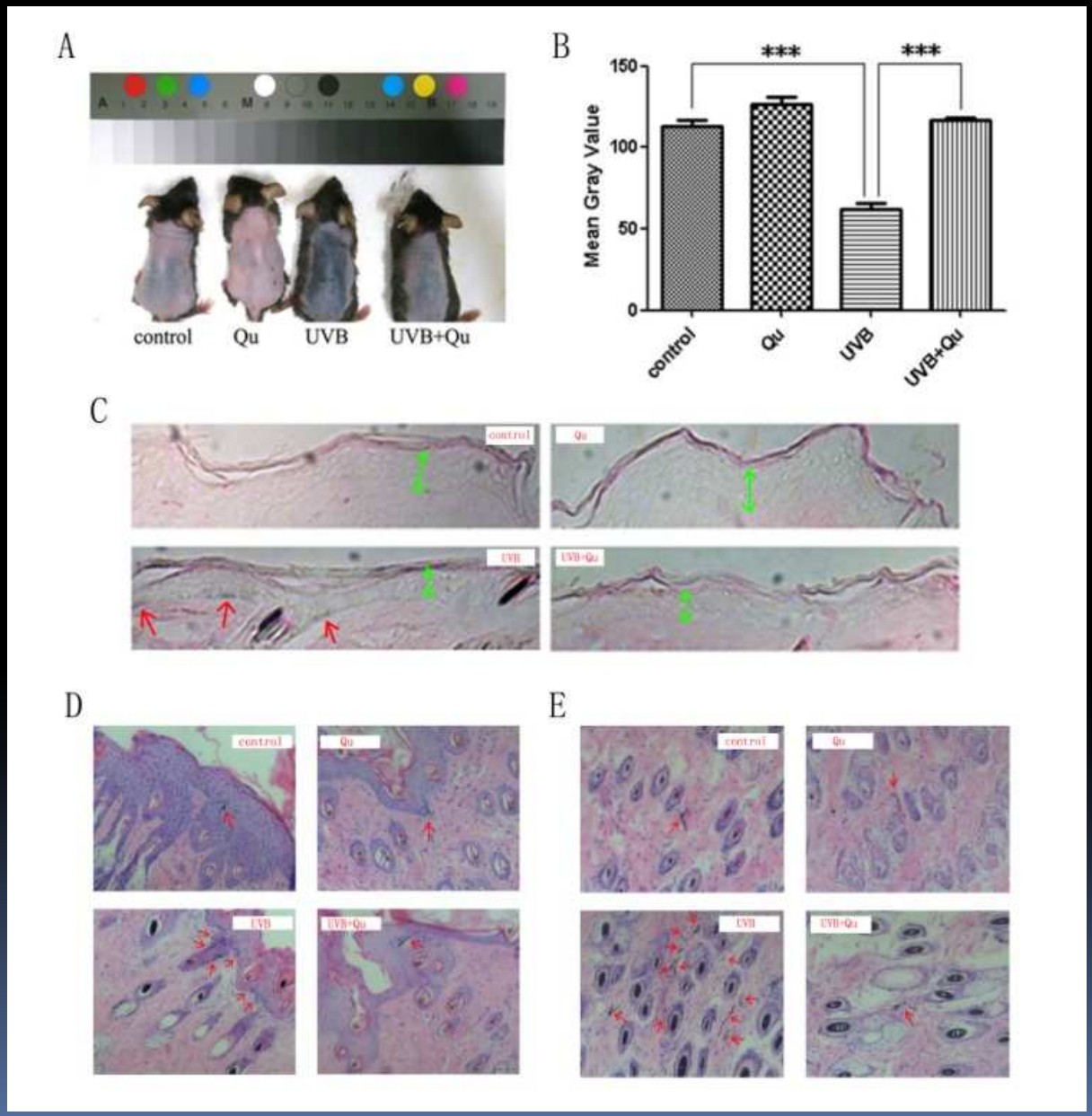
植物黄酮类成分

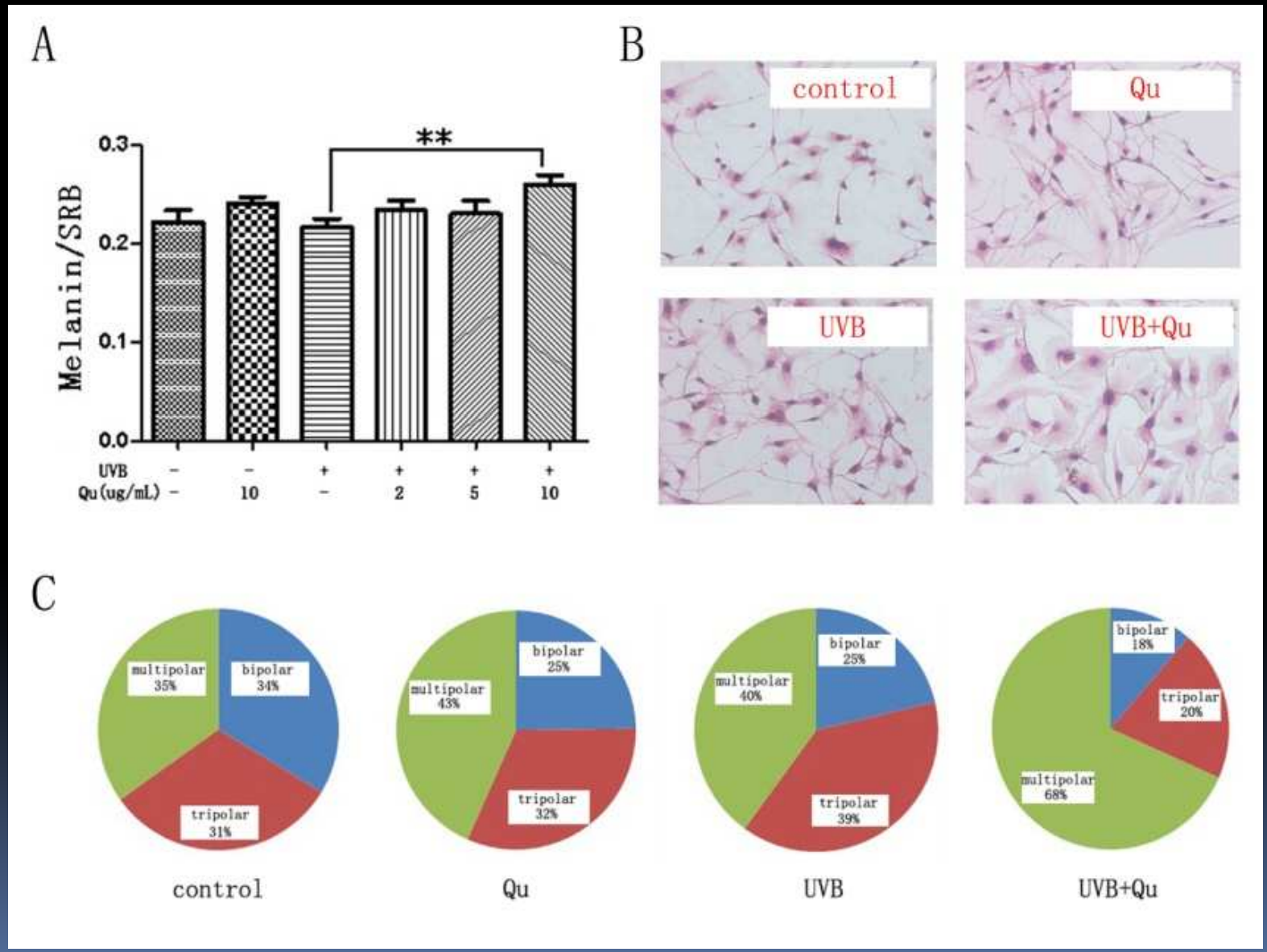
仿生生物学原理

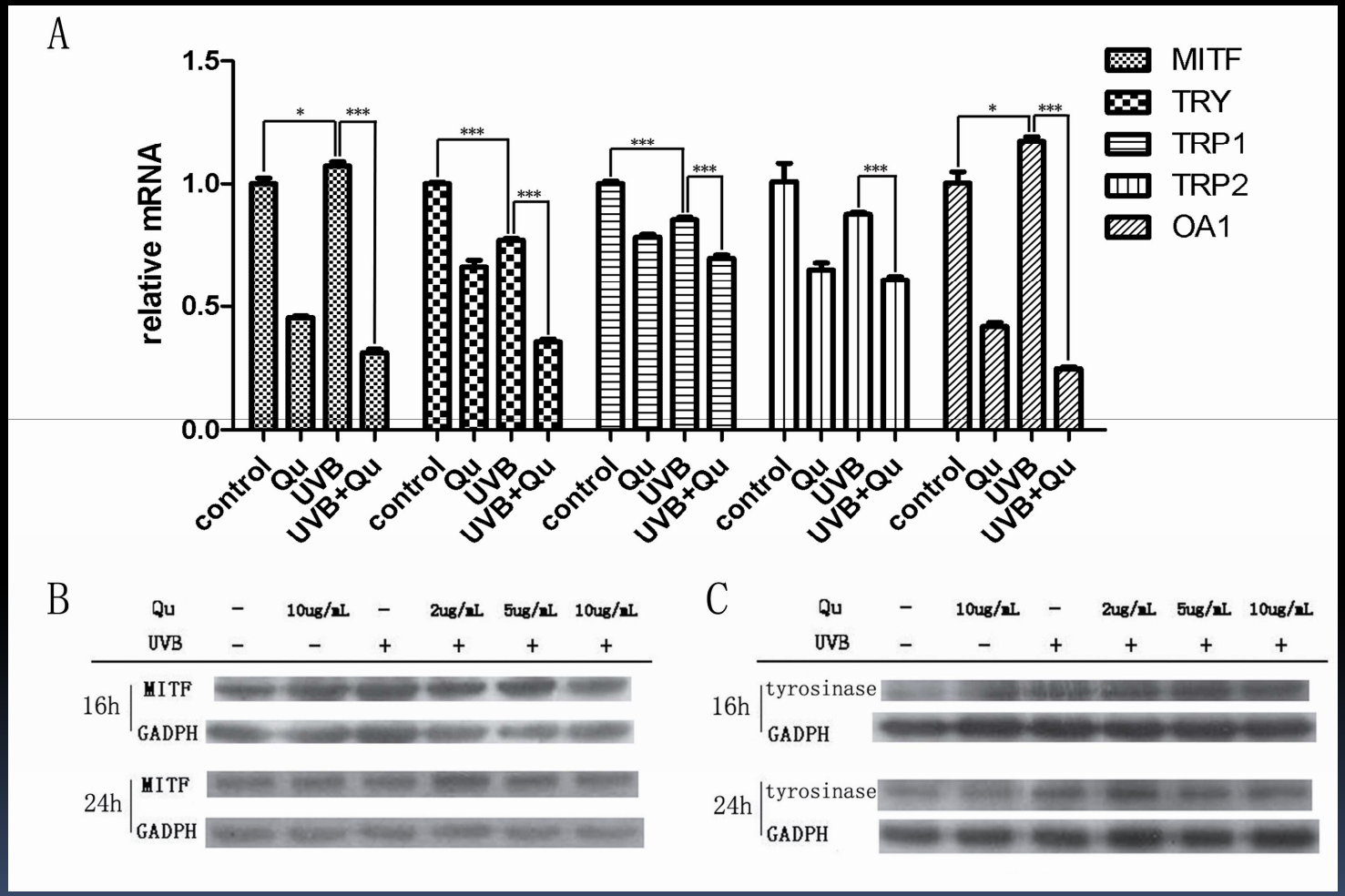


体内外实验模型建立

Cell: Melan-a
C57/6BL mouse, female， 7-8 weeks
将黑鼠背部剃毛，然后（对照/涂药）经UVB照射

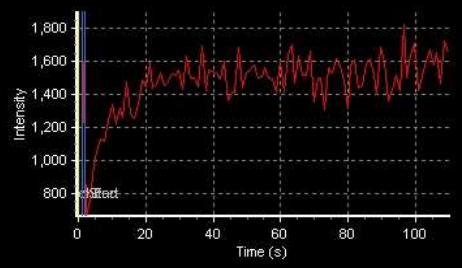

A
control
Qu
UVB
UVB+Qu
B
***
***
150
100
50
0
Mean Gray Value
control
Qu
UVB
UVB+Qu
C
control
Qu
UVB
UVB+Qu
D
control
Qu
UVB
UVB+Qu
E
control
Qu
UVB
UVB+Qu

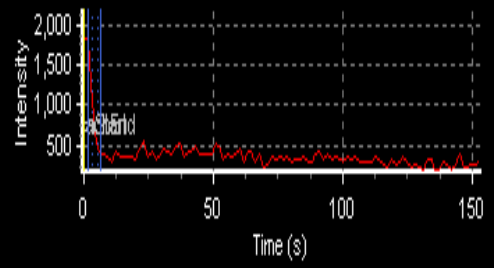

A
Melanin/SRB
0.3
0.2
0.1
0.0
**
UVB - - + + + +
Qu(ug/mL) - 10 - 2 5 10
B
control
Qu
UVB
UVB+Qu
C
multipolar 35%
bipolar 34%
tripolar 31%
control
multipolar 43%
bipolar 25%
tripolar 32%
Qu
multipolar 40%
bipolar 25%
tripolar 39%
UVB
bipolar 18%
tripolar 20%
multipolar 68%
UVB+Qu

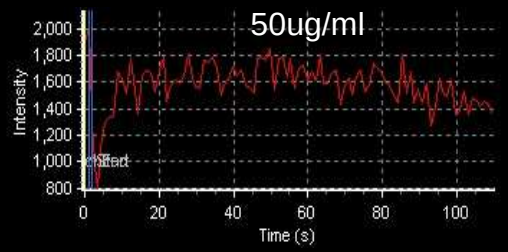

A
relative mRNA
1.5
1.0
0.5
0.0
MITF
TRY
TRP1
TRP2
OA1
control
Qu
UVB
UVB+Qu
B
Qu
10ug/mL
2ug/mL
5ug/mL
10ug/mL
UVB
16h
24h
MITF
GADPH
C
tyrosinase
GADPH

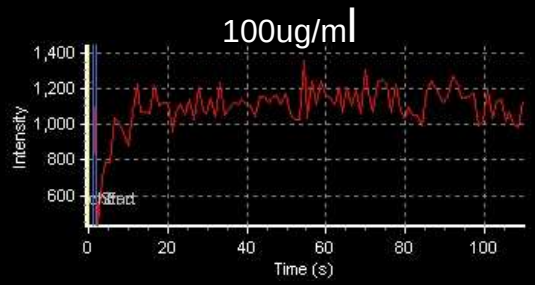
细胞膜流动性化机理

荧光光漂白恢复（FRAP）技术检测细胞膜流动性的变化情况









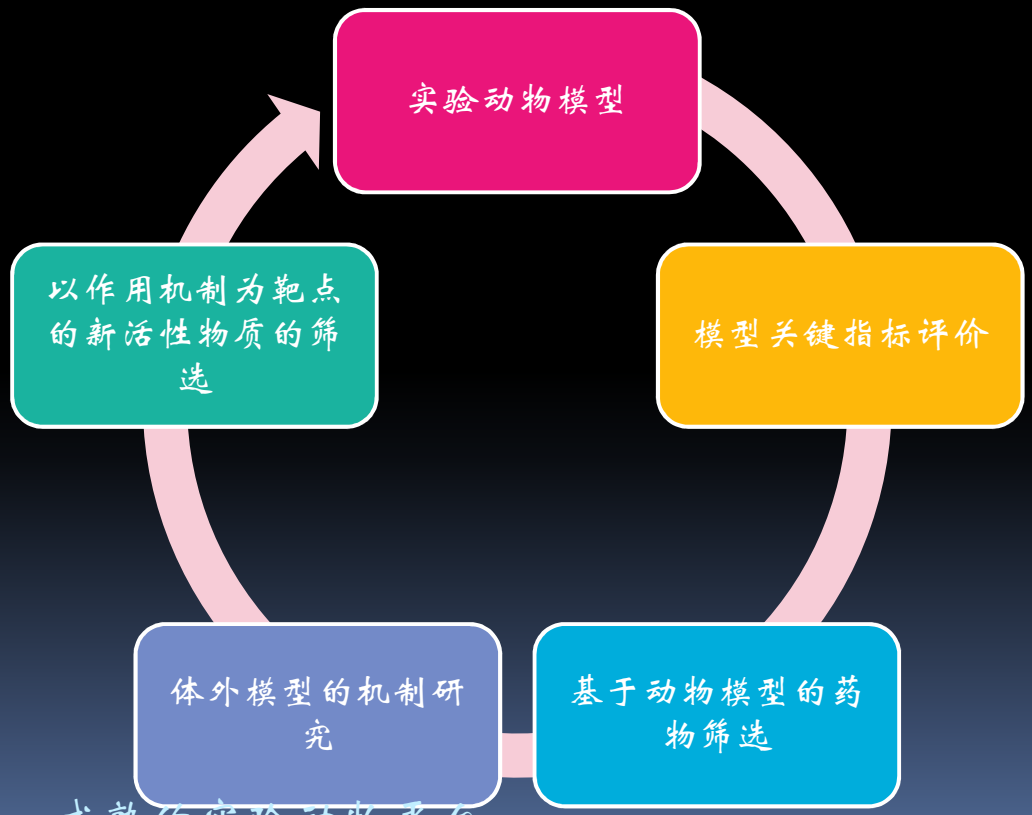
细胞膜流动性恢复率数据统计分析

四、应用展望

1、药理药效确定：体内外实验模型选择;

2、制剂手段 药用材料以及合适剂型选择 提高与皮肤粘合力;

3、选择合适的药材及提取物



成熟的实验动物平台